SPRINGER NATURE
Sustainable Development Goals Series

SDG: 3
Good Health and Well-being

Geraldo Bezerra da Silva Junior
Elizabeth De Francesco Daher
Elvino Barros *Editors*

Tropical Nephrology

Second Edition

Springer

Sustainable Development Goals Series

The **Sustainable Development Goals Series** is Springer Nature's inaugural cross-imprint book series that addresses and supports the United Nations' seventeen Sustainable Development Goals. The series fosters comprehensive research focused on these global targets and endeavours to address some of society's greatest grand challenges. The SDGs are inherently multidisciplinary, and they bring people working across different fields together and working towards a common goal. In this spirit, the Sustainable Development Goals series is the first at Springer Nature to publish books under both the Springer and Palgrave Macmillan imprints, bringing the strengths of our imprints together.

The Sustainable Development Goals Series is organized into eighteen subseries: one subseries based around each of the seventeen respective Sustainable Development Goals, and an eighteenth subseries, "Connecting the Goals", which serves as a home for volumes addressing multiple goals or studying the SDGs as a whole. Each subseries is guided by an expert Subseries Advisor with years or decades of experience studying and addressing core components of their respective Goal.

The SDG Series has a remit as broad as the SDGs themselves, and contributions are welcome from scientists, academics, policymakers, and researchers working in fields related to any of the seventeen goals. If you are interested in contributing a monograph or curated volume to the series, please contact the Publishers: Zachary Romano [Springer; zachary.romano@springer.com] and Rachael Ballard [Palgrave Macmillan; rachael.ballard@palgrave.com].

Geraldo Bezerra da Silva Junior
Elizabeth De Francesco Daher
Elvino Barros
Editors

Tropical Nephrology

Second Edition

Springer

Editors
Geraldo Bezerra da Silva Junior
Post-Graduation Programs in Public Health and Medical Sciences,
School of Medicine
University of Fortaleza
Fortaleza, Ceará, Brazil

Elizabeth De Francesco Daher
Department of Internal Medicine,
School of Medicine
Universidade Federal do Ceará
Fortaleza, Ceará, Brazil

Elvino Barros
Federal University of Rio Grande do Sul
Porto Alegre, Rio Grande do Sul, Brazil

Color wheel and icons: From https://www.un.org/sustainabledevelopment/
Copyright © 2020 United Nations. Used with the permission of the United Nations.
The content of this publication has not been approved by the United Nations and does not reflect the views of the United Nations or its officials or Member States.

ISSN 2523-3084 ISSN 2523-3092 (electronic)
Sustainable Development Goals Series
ISBN 978-3-031-94776-6 ISBN 978-3-031-94777-3 (eBook)
https://doi.org/10.1007/978-3-031-94777-3

© The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Switzerland AG 2020, 2025

This work is subject to copyright. All rights are solely and exclusively licensed by the Publisher, whether the whole or part of the material is concerned, specifically the rights of reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

If disposing of this product, please recycle the paper.

Foreword to Second Edition, 2025

It is with great honor that, five years after the release of the first edition of this work, I accepted the invitation to write the preface for the second edition of *Tropical Nephrology*, an essential resource for researchers and professionals working in this important area of human health.

This edition includes new chapters addressing topics such as climate change, the use of medicinal herbs, Haff disease, and tropical diseases in transplant patients, as well as updates to the chapters from the previous edition. It reinforces the importance of the association between tropical diseases—like malaria, schistosomiasis, leptospirosis, and leishmaniasis, which are prevalent in warm climates—and their impact on kidney health, further complicated by sanitary, environmental, and socioeconomic factors.

Nephrology and tropical medicine, though distinct medical specialties, are intrinsically linked when it comes to healthcare for populations, particularly those in socially vulnerable conditions. Both are critically relevant in contexts where socioeconomic and environmental issues heighten disease risk, exacerbating the plight of individuals in precarious situations. Understanding the relationship between these areas is vital for developing medical approaches and public health policies aimed at improving living conditions and providing appropriate treatment for these populations.

"Disease has an initiatory function: through it, we can come to a greater understanding of ourselves," reflected Rubem Alves on the role of chronic illness. Self-knowledge, an awareness of one's surroundings, and effective prevention and management methods are the necessary tools to control the aggravation of undesirable conditions and to enable a better quality of life.

The guiding theme of the research compiled here highlights the multitude of factors that can explain the high prevalence of this issue in this region of the planet, even though it should be a historical record of a bygone scourge.

For instance, leptospirosis causes typical damage to kidney tissues, which can lead to kidney injury. Malaria is no different.

I could also mention glomerulonephritis—one of the consequences of schistosomiasis; the excessive use of nephrotoxic drugs used to combat certain diseases that seriously impair kidney function; dehydration caused by lack of access to quality drinking water; overweight issues due to inadequate nutrition and lack of physical exercise, all of which are significant.

It is important to remember that the rapidity of climate change in some parts of the planet, the lack of access to serious health education policies, and the economic disparities, as noted in the 2021 WHO Climate Change and

Health Report, explain the alarming rates of illness, particularly in kidney medicine.

Sir Patrick Manson, a nineteenth-century Scottish physician and researcher, known for his pioneering contributions to tropical medicine, especially in studying parasitic diseases and understanding the role of vectors in disease transmission, viewed tropical medicine not merely as a means of healing but as a way to understand and respect these complex relationships.

Sorensen (2020), a prominent researcher in the field, states that "human health is deeply connected to the health of our planet, and protecting both is an urgent priority." Therefore, beyond describing the cases observed, this work is also a call for the adoption of methods that not only address symptom management but also raise awareness among authorities, civil society, the press, and health professionals about adopting climate policies that necessarily involve greater public health education.

Updated data from the World Health Organization (WHO) shows that around the world, about 2 billion people lack regular access to safe drinking water. Diets high in sodium and low in nutrients—more accessible to lower-income individuals—also increase the risk of hypertension and diabetes, which, as is known, are gateways to nephrological diseases and are often neglected, as are tropical diseases in developing countries.

In light of the need for quality information in this unending battle, I congratulate every researcher who, with care and dedication, brings to light this collection of studies that comprise this book. May they be prosperous, advancing in the field of science and research, which, as we know, has the power to improve the lives of this generation and leave future generations a less hostile and healthier world.

Natalino Salgado Filho

Full Professor, School of Medicine
at the Federal University of Maranhão – UFMA
São Luís, Brazil

Head of Urinary System
University Hospital HU – UFMA
São Luís, Brazil

Coordinator of Clinical Research
in Nephrology – HU – UFMA
São Luís, Brazil

Coordinator of League of Kidney
Diseases – HU – UFMA
São Luís, Brazil

Foreword to First Edition, 2020

Since the publication of English naturalist Charles Darwin's *On the Origin of Species* in 1859, it has been known that every living organism has a close relation ship with its environment, through what Darwin termed "descent with modification" by the mechanism of natural selection, which was later to be called the theory of evolution. This is as true for multicellular organisms as it is for all others, at different adaptive velocities.

This assumption suggests the need for studies that identify the actual association between kidney disease in individuals in the tropics and the diseases involved in these environmental conditions. That said, we believe this book does an excellent job of contextualizing kidney disease in the tropical latitudes and, particularly, in the Brazilian scenario.

The book *Tropical Nephrology* fills a gap that is absolutely necessary to under- stand kidney disease and its many associations with diseases that are characteristic of tropical areas, which coincides not only with many of their endemic characteris tics but especially with the precarious socioeconomic status of countries in this region of the world, thus severely affecting the health services available to their populations.

Although the World Health Organization's report—*Integrating Neglected Tropical Diseases in Global Health and Development*—published in 2017 is quite optimistic about the advances made during the last 10 years in relation to what they call "neglected tropical diseases" (NTDs), the situation is still extremely alarming, even in a country such as Brazil, which, despite the universal health coverage provided by the Unified Health System like primary care services, vaccination campaigns, and drug distribution, still suffers from poor regional distribution of professionals and services. In addition, the country has to deal with basic sanitation issues, and also the outbreak of recent epidemics of previously controlled tropical diseases, or somewhat unexpected ones, such as the Zika and Chikungunya epidemics.

The aforementioned report indicates that millions of individuals in Latin American countries are at risk from several diseases, some of which are manageable through simple measures, although accessible at different degrees in these countries.

The scope of this study establishes a very important parameter for the study of kidney disease. The different scenarios presented in the chapters show that research in Brazil, in spite of all known limitations, yields results that are relevant to knowledge. This is one of the merits of this work, which is to present the diversity of views having as the background kidney disease

and its interactions with health problems, which, unfortunately, are still on the agenda in our health system.

Considering the scarcity of resources and the growing number of individuals with some degree of kidney disease—the vast majority of which are undiagnosed or, due to exposures to tropical diseases, have underdiagnosed kidney conditions that become aggravated and chronic—this work provides a good starting point and opens up, for instance, the possibility for future studies that will consider the economic aspect and will perhaps apply the DALY (disability-adjusted life years) concept to our reality, which each tropical disease imposes on populations. Whether in preventive or curative programs, to adequately define this concept and combine it with kidney disease can be helpful at any given time and place, especially where resources can achieve their best results.

I want to congratulate the willingness and the efforts of all who contributed to the creation of this work, its collaborating authors and organizers. The scientific quality of the material, added to the experience and ability of all those who dedicated themselves to making this material available, shows the indispensability of its careful reading.

I would also like to congratulate the creators of this magnificent work, particularly the editors Geraldo Bezerra da Silva Junior, Elizabeth De Francesco Daher, and Elvino Barros of the Brazilian Society of Nephrology for their contribution to the world.

Natalino Salgado Filho

Full Professor of Nephrology
at the Federal University of Maranhão
Full Member of the National Academy
of Medicine Member of the Brazilian Academy
of Medicine and Academy of Letters of Maranhão
São Luís, Brazil

Contents

Part I The Impacts of Today's World on Tropical Diseases and Kidney Health

1 Tropical Diseases: A Public Health Problem with Impact on Nephrology 3
Prit Kusirisin, Visith Sitprija, and Nattachai Srisawat

2 Climate Change and the Risk of Illness 19
Clara Beatriz Costa da Silva, Tibelle Freitas Mauricio, Tainara Chagas de Sousa, Vanessa Emille Carvalho de Sousa Freire, Tahissa Frota Cavalcante, Alexandre Cunha Costa, and Rafaella Pessoa Moreira

3 Climate Change in the Tropics: Rising Temperatures and Kidney Health 29
Fabiana Baggio Nerbass, Jyana Gomes Morais, and Marcos Alexandre Vieira

Part II Kidney Diseases Associated to Environmental Factors and Exogenous Agents

4 Environmental Factors Causing Kidney Diseases 41
Edgar Sanclemente-Paz, David Ballesteros, and Giovanni Apraez

5 Nephropathy Due to Exogenous Poisoning. 65
Alice Maria Costa Martins, Gdayllon Cavalcante Meneses, Polianna Lemos Moura Moreira Albuquerque, Nicole Coelho Lopes, Igor Moreira de Almeida, Leticia Machado de Araujo, and Bruna Viana Barroso Martins

6 Nephropathy Associated with the Use of Herbal Medicine. 77
Rolando Claure-Del Granado, Jonathan S. Chávez-Íñiguez, and Maria de Los Ángeles Espinosa-Cuevas

7 Haff Disease 85
Karla Cristina Petruccelli Israel, Mathias Alberto Schramm, Tatyana Costa Amorim Ramos, Michael do Nascimento Correia, Felipe Costa Neves, and Polianna Lemos Moura Moreira Albuquerque

Part III Kidney Diseases Associated to Venomous Animals

8 Kidney Complications in Bothropic and Crotalic Envenomation 97
Jacqueline de Almeida Gonçalves Sachett, Marco Aurélio Sartim, Manuela Pucca, Lisele Brasileiro Martins, Thaís Pinto Nascimento, Valquir Silva dos Santos, Marcus Vinícius Guimarães de Lacerda, and Wuelton Marcelo Monteiro

9 Nephropathy Caused by Scorpion Stings 113
Edgar Sanclemente-Paz

10 Spider Bite Nephropathy 121
Edgar Sanclemente-Paz

11 Kidney Injuries Secondary to Ant Bites 127
Edgar Sanclemente-Paz

12 Kidney Injury Caused by Marine Toxins 131
Edgar Sanclemente-Paz

13 Hemorrhagic Accidents Caused by *Lonomia obliqua* 139
Alaour Candida Duarte, Verônica Verleine Hörbe Antunes, Elvino Barros, Gabriela Vieira Steckert, Gabriel Sartori Pacini, and Renata Asnis Schuchmann

Part IV Virus-Associated Kidney Diseases

14 Kidney Involvement in Arboviral Diseases: Chikungunya, Dengue, and Zika 147
Roberto da Justa Pires Neto, Denise Maria do Nascimento Costa, and Geraldo Bezerra da Silva Junior

15 Acute Kidney Injury in Yellow Fever 161
Cassia Fernanda Estofolete, Rodrigo José Ramalho, Horácio José Ramalho, and Mauricio Lacerda Nogueira

16 Hantavirus and the Kidneys 165
Carlos Ramiro Silva Ramos, Álvaro A. Faccini-Martínez, and Stefan Vilges de Oliveira

17 HIV and Kidney Disease 183
Geraldo Bezerra da Silva Junior,
Juliana Gomes Ramalho
de Oliveira, Elizabeth De Francesco Daher,
and Saraladevi Naicker

18 Viral Hepatitis and Kidney Disease 195
Elodie Bomfim Hyppolito, Roberto da Justa Pires Neto,
and Geraldo Bezerra da Silva Junior

19 Nephropathy Due to Influenza A (H1N1) Infection 211
Edgar Sanclemente-Paz

Part V Kidney Diseases Associated with Parasitic Agents

20 Kidney Involvement in Chagas' Disease (American Trypanosomiasis) 217
Elizabeth De Francesco Daher, Geraldo Bezerra da Silva Junior,
Elvino Barros, João Filipe Cavalcante Uchoa Furtado,
Pedro Vianna Caldas Ribeiro, Verônica Verleine Hörbe Antunes,
Gabriela Vieira Steckert, Gabriel Sartori Pacini,
and Renata Asnis Schuchmann

21 Kidney Disease Associated with *Schistosomiasis Mansoni* 225
Daniella Bezerra Duarte, Elizabeth De Francesco Daher,
Maria Eliete Pinheiro, and Michelle Jacintha Cavalcante
Oliveira

22 Lymphatic Filariasis Nephropathy 239
Maria Eliete Pinheiro, Daniella Bezerra Duarte,
Michelle Jacintha Cavalcante Oliveira, and Gilberto Fontes

23 Kidney Involvement in American Cutaneous Leishmaniasis . . . 253
Rodrigo Alves de Oliveira, Guilherme Alves de Lima Henn,
Paulo Sérgio Ramos de Araújo,
and Claudio Gleidston Lima da Silva

24 Nephropathy in Visceral Leishmaniasis (Kala-Azar) 267
Gdayllon Cavalcante Meneses, Guilherme Alves de Lima Henn,
Alice Maria Costa Martins,
Michelle Jacintha Cavalcante Oliveira,
and Elizabeth De Francesco Daher

25 Malaria and Kidney Complications 279
Karla Cristina Silva Petruccelli, Valquir Silva dos Santos,
Alba Regina Jorge Brandão, Izabella Picinin Safe Lacerda,
Fernando Fonseca de Almeida e Val,
and Marcus Vinícius Guimarães de Lacerda

Part VI Kidney Diseases Associated with Bacteria

26 Post-streptococcal and Epidemic Glomerulonephritis 291
Artur Quintiliano Bezerra da Silva
and Gianna Mastroianni Kirsztajn

27 Staphylococcal Infections and Kidney Disease. 301
Maria Almerinda Vieira Fernandes Ribeiro Alves

28 Leprosy Nephropathy 307
Verônica Verleine Hörbe Antunes, Elvino Barros,
Geraldo Bezerra da Silva Junior, Alice Maria Costa Martins,
Gdayllon Cavalcante Meneses, Elizabeth De Francesco Daher,
João Filipe Cavalcante Uchoa Furtado,
Pedro Vianna Caldas Ribeiro, Ariana Custódio Vieira,
and Juliana Hickmann de Moura

29 Leptospirosis and the Weil's Syndrome 315
Gabriela Studart Galdino, Geraldo Bezerra da Silva Junior,
Elizabeth De Francesco Daher, Elvino Barros,
Arthur Gus Manfro, Vanderlei Carlos Bertuol Junior,
João Filipe Cavalcante Uchoa Furtado,
and Pedro Vianna Caldas Ribeiro

30 Acute Kidney Injury in Tetanus 323
Geraldo Bezerra da Silva Junior,
Juliana Gomes Ramalho de Oliveira,
Guilherme Alves de Lima Henn, Gustavo Mandelli,
Pedro Guimarães Pascoal,
João Filipe Cavalcante Uchoa Furtado,
Pedro Vianna Caldas Ribeiro, and Elizabeth De Francesco Daher

31 Renal Tuberculosis 331
Rafael Siqueira Athayde Lima, Geraldo Bezerra da Silva Junior,
João Filipe Cavalcante Uchoa Furtado,
Pedro Vianna Caldas Ribeiro, Elvino Barros,
and Elizabeth De Francesco Daher

32 Syphilitic Nephropathy. 339
Romélia Pinheiro Gonçalves Lemes,
Suzzy Maria Carvalho Dantas, Igor Ribeiro de Lemos,
João Filipe Cavalcante Uchoa Furtado,
Pedro Vianna Caldas Ribeiro, Elizabeth De Francesco Daher,
and Geraldo Bezerra da Silva Junior

Part VII Chronic Diseases, Transplantation and Interface with Tropical Nephrology

33 Kidney Function Evaluation in Tropical Diseases 351
Geraldo Bezerra da Silva Junior, Elvino Barros, Gabriela Moreira Ferle, Pedro Guimarães Pascoal, João Filipe Cavalcante Uchoa Furtado, Pedro Vianna Caldas Ribeiro, Elizabeth De Francesco Daher, and Francisco Veríssimo Veronese

34 Kidney Disease of Unknown Origin and Tropical Diseases 359
Maristela Böhlke, Viviane Calice-Silva, Eduardo Ribes Kohn, Pedro Böhlke Barcellos, Carmen Lorena Cajina Aguirre, and Roberto Pecoits-Filho

35 Tropical Diseases in Kidney Transplantation 371
Lucio Requião Moura, Silvana Daher Costa, and Taina Veras de Sandes-Freitas

Index 391

About the Editors and Contributors

Editors

Geraldo Bezerra da Silva Junior Nephrologist. Master and PhD in Medical Sciences at the Federal University of Ceara, Brazil. Postdoctoral fellowship in Public Health/Epidemiology at the Federal University of Bahia. Full Professor at the University of Fortaleza. Director of the Department of Epidemiology and Prevention of Kidney Disease and Coordinator of the Academic Leagues Committee of the Brazilian Society of Nephrology. Fellow of the International Society of Nephrology. Member of the Young Medical Leaders Program of the National Academy of Medicine, Brazil.

Elizabeth De Francesco Daher Nephrologist. PhD in Nephrology at the University of Sao Paulo. Full Professor at the Federal University of Ceara, Brazil. Member of the Department of Education and Titling of the Brazilian Society of Nephrology.

Elvino Barros Nephrologist. PhD in Nephrology at the Federal University of Sao Paulo. Associate Professor at the Federal University of Rio Grande do Sul, Brazil.

Contributors

Polianna Lemos Moura Moreira Albuquerque Nephrologist. PhD in Medical Sciences from the Federal University of Ceará, Brazil. Senior Lecturer in Biomedical Sciences, Faculty of Health, Charles Darwin University, Darwin, Northern Territory, Australia.

Maria Almerinda Vieira Fernandes Ribeiro Alves Nephrologist. Master in Internal Medicine and PhD in Medicine/Nephrology from the Federal University of São Paulo. Assistant professor at the State University of Campinas, São Paulo, Brazil.

Verônica Verleine Hörbe Antunes Nephrologist. Master in Medicine/Nephrology from the Federal University of Rio Grande do Sul; Supervisor of the Medical Residency Program in Nephrology at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil.

Giovanni Apraez Department of Public Health, Faculty of Medicine, National University of Colombia, Bogota D.E., Colombia.

David Ballesteros Nephrologist. Department of Internal Medicine, Faculty of Medicine, University of Cauca, Popayán, Cauca, Colombia.

Pedro Böhlke Barcellos Medical student at the Catholic University of Pelotas, Rio Grande do Sul, Brazil.

Elvino Barros Nephrologist. PhD in Nephrology at the Federal University of Sao Paulo. Associate Professor at the Federal University of Rio Grande do Sul, Brazil.

Geraldo Bezerra da Silva Junior Nephrologist. Master and PhD in Medical Sciences at the Federal University of Ceara, Brazil. Postdoctoral fellowship in Public Health/Epidemiology at the Federal University of Bahia. Full Professor at the University of Fortaleza. Director of the Department of Epidemiology and Prevention of Kidney Disease and Coordinator of the Academic Leagues Committee of the Brazilian Society of Nephrology. Fellow of the International Society of Nephrology. Member of the Young Medical Leaders Program of the National Academy of Medicine, Brazil.

Maristela Böhlke Nephrologist. Master in Medine/Health Sciences from the Pontifical Catholic University of Rio Grande do Sul and PhD in Nephrology from the Federal University of São Paulo, Brazil. Adjunct professor at the Catholic University of Pelotas, Rio Grande do Sul, Brazil.

Alba Regina Jorge Brandão Nephrologist. Postgraduate in Neurointensivism from the Syrian Lebanese Hospital, São Paulo, Brazil. PhD in Tropical Medicine from the State University of Amazonas, Dr. Heitor Vieira Dourado Tropical Medicine Foundation, Brazil.

Carmen Lorena Cajina Aguirre Medical Doctor. The University of Kansas Medical Center, Kansas City, Kansas, USA.

Viviane Calice-Silva Nephrologist. PhD in Health Sciences from the Pontifical Catholic University of Paraná. Postdoctoral fellowship in Epidemiology and Clinical Research at University of São Paulo, Brazil. Professor of Nephrology at the Specialties Outpatient Clinic at the Univille School of Medicine and preceptor of nephrology residence at Pro-Rim Foundation and Hospital Hans Dieter Schimidt, Joinville, Santa Catarina, Brazil.

Tahissa Frota Cavalcante Adjunct Professor of the Nursing and the Postgraduate Program in Nursing at the University of International Integration of Afro-Brazilian Lusophony (UNILAB), Brazil. Post-Doctorate in Nursing et the Federal University of Ceara. Coordinator of the Postgraduate Program in Nursing at UNILAB. Member of the Nursing Process Research Network (RePPE). Member of the Climate Change Task Force—NANDA-I.

Jonathan S. Chávez-Íñiguez Nephrology Service, Fray Antonio Alcalde Civil Hospital of Guadalajara, Guadalajara, Jalisco. Mexico; University of Guadalajara Health Sciences Center, Guadalajara, Jalisco. Mexico.

Rolando Claure-Del Granado Division of Nephrology, Hospital Obrero No 2 - Caja Nacional de Salud, Cochabamba, Bolivia.

Alexandre Cunha Costa Adjunct Professor at the Institute of Engineering and Sustainable Development of the University of International Integration of Afro-Brazilian Lusophony (UNILAB), Brazil. Postdoctoral fellowship at the Federal University of Ceara, Brazil. Visiting Researcher at the Wageningen University, The Netherlands. Member of the Brazilian Water Resources Association, contributing to the Technical Committee on Disasters. Member of the Climate Change Task Force—NANDA-I.

Denise Maria do Nascimento Costa Nephrologist and Preceptor of the Medical Residency in Nephrology at University Hospital—Federal University of Pernambuco. Adjunct Professor of the Department of Internal Medicine—Faculty of Medicine of Recife—Federal University of Pernambuco. Master degree in Health Sciences and PhD in Tropical Medicine from the Federal University of Pernambuco, Brazil.

Silvana Daher Costa Nephrologist. Master and PhD in Medical Sciences from the Federal University of Ceará. Physician in the kidney transplant and nephrology sectors at the Federal University of Ceará and General Hospital of Fortaleza, Brazil.

Elizabeth De Francesco Daher Nephrologist. PhD in Nephrology at the University of Sao Paulo. Full Professor at the Federal University of Ceara, Brazil. Member of the Department of Education and Titling of the Brazilian Society of Nephrology.

Roberto da Justa Pires Neto Medical Doctor, specialist in Internal Medicine and Infectious Diseases. Master and PhD in Medicine/Medical Sciences from the School of Medicine of Ribeirão Preto, University of São Paulo. Associate Professor in the Department of Community Health, School of Medicine, Federal University of Ceará, Brazil.

Suzzy Maria Carvalho Dantas Pharmacist. Master in Pathology, Federal University of Ceará. Pharmacist at the Laboratory of Hemoglobinopathies and Genetics of Hematological Diseases, Federal University of Ceará, Brazil.

Artur Quintiliano Bezerra da Silva Nephrologist. Master and PhD from the Federal University of São Paulo. Professor at the Federal University of Rio Grande do Norte, Brazil.

Clara Beatriz Costa da Silva Master in Nursing at the University of International Integration of Afro-Brazilian Lusophony (UNILAB), scholarship holder of the Coordination for the Improvement of Higher Education Personnel—CAPES, Brazil. Graduated in Nursing from UNILAB. Member of the Research and Extension Group Nursing Care Technologies in the Scenario of Chronic Diseases, Brazil.

Claudio Gleidston Lima da Silva Medical Doctor from the Federal University of Ceará. Master in Pathology and PhD in Pharmacology from the Federal University of Ceará. Postdoctoral fellowship at the ABC Medical School, São Paulo, Brazil. Associate Professor at the Federal University of Cariri, Juazeiro do Norte, Ceará, Brazil.

Fernando Fonseca de Almeida e Val Physiotherapist from the University of São Paulo. PhD in Tropical from the Amazonas State University. Physiotherapist at the intensive care unit of the Dr. Heitor Vieira Dourado, Hospital Unit in Manaus, Amazonas, Brazil. Professor at the Postgraduate Program in Health Sciences and the Graduate Program in Human Movement Sciences at the Federal University of Amazonas, Brazil.

Jacqueline de Almeida Gonçalves Sachett Nurse from the Federal University of Juiz de Fora; Master in Nursing from the Federal University of Minas Gerais and PhD in Tropical and Infectious Diseases from the State University of Amazonas. Adjunct Professor of the Undergraduate Nursing course at the State University of Amazonas, Brazil.

Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil
Universidade do Estado do Amazonas, Manaus, Amazonas, Brazil

Igor Moreira de Almeida Pharmacist. Master in Pharmacology at the Federal University of Ceará, Brazil.

Letícia Machado de Araújo Pharmacy student from the Federal University of Ceará, Brazil. Scholarship holder at the Pharmaceutical Bioprospecting and Clinical Biochemistry Laboratory, Brazilian Research Council (CNPq).

Paulo Sérgio Ramos de Araújo Medical Doctor from the University of Pernambuco, Master and PhD in Tropical Medicine from the Federal University of Pernambuco. Associate Professor at the Federal University of Pernambuco, Brazil.

Marcus Vinícius Guimarães de Lacerda Medical Doctor from the University of Brasília, specialization in Infectology from the Dr. Heitor Vieira Dourado Foundation for Tropical Medicine and PhD in Tropical Medicine from the University of Brasília. Researcher at Dr. Heitor Vieira Dourado Foundation for Tropical Medicine, professor in the Postgraduate Program in

Tropical Medicine at the State University of Amazonas, Brazil, and adjunct professor at the University of Texas Medical Branch, USA.
Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil
Instituto Leônidas & Maria Deane (ILMD/Fiocruz Amazônia), Manaus, Amazonas, Brazil
Post-Graduation Program in Tropical Medicine, Tropical Medicine Foundation Dr. Heitor Vieira Dourado, State University of Amazonas, Manaus, Amazonas, Brazil

Igor Ribeiro de Lemos Medical student at the Federal University of Ceará, Brazil.

Guilherme Alves de Lima Henn Medical Doctor, specialist in Infectology. Master in Public Health from the Federal University of Ceará. Physician at the São José Infectious Diseases Hospital and Hospital Geral de Fortaleza (HGF). Professor at the School of Medicine, Federal University of Ceará, Brazil.

Maria de Los Ángeles Espinosa-Cuevas Department of Nephrology and Mineral Metabolism, National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City, Mexico.

Juliana Hickmann de Moura Medical Doctor from the Vale do Itajaí University. Nephrology residency at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil.

Juliana Gomes Ramalho de Oliveira Nurse graduated from the University of Fortaleza; Specialization in Nephrology Nursing from the State University of Ceará; Master and PhD in Public Health from the University of Fortaleza, Brazil.

Rodrigo Alves de Oliveira Nephrologist. Master in Medicine/Internal Medicine and a PhD in Medical Sciences from the Federal University of Ceará. Adjunct professor of the School of Medicine at the Agreste Campus of the Federal University of Pernambuco, Brazil.

Stefan Vilges de Oliveira Graduated in Biological Sciences from the University of the Region of Campanha, specialization in Ecology from the Federal University of Rio Grande, master degree and PhD in Tropical Medicine from University of Brasília. Adjunct Professor at the Department of Coletive Health at the School of Medicine at the Federal University of Uberlândia, Brazil.

Taina Veras de Sandes-Freitas Nephrologist. Master and PhD in Medicine/Nephrology from the Federal University of São Paulo. Postdoctoral fellowship at the Federal University of São Paulo. Adjunct Professor at the Federal University of Ceará, Brazil.

Vanessa Emille Carvalho de Sousa Freire Visiting Researcher at the University of International Integration of Afro-Brazilian Lusophony (UNILAB), Brazil. PhD in Nursing at the Federal University of Ceara, with a sandwich period at the University of Illinois at Chicago, USA. Postdoctoral fellowship at the University of Illinois at Chicago, USA. Member of the Climate Change Task Force—NANDA-I.

Tainara Chagas de Sousa Nursing student at the University of International Integration of Afro-Brazilian Lusophony (UNILAB), Brazil. Scientific Initiation Scholarship holder. Member of the Research and Extension Group Nursing Care Technologies in the Scenario of Chronic Diseases, Brazil.

Michael do Nascimento Correia Medical Doctor from the State University of Amazonas. Technical Director of the José Mendes Regional Hospital, Itacoatiara-Amazonas, Brazil.

Valquir Silva dos Santos Medical Doctor from the Federal University of Amazonas. Medical Residency in Clinical Medicine from the Getúlio Vargas University Hospital and Nephrology from the Getúlio Vargas University Hospital. Physician at the Dr. Heitor Vieira Dourado Tropical Medicine Foundation, Amazonas, Brazil.

Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil
Division of Nephrology, Tropical Medicine Foundation Dr. Heitor Vieira Dourado, Manaus, Amazonas, Brazil

Alaour Candida Duarte Nephrologist. Master in Medicine/Nephrology from the Federal University of Rio Grande do Sul, Brazil.

Daniella Bezerra Duarte Nephrologist. PhD in Medical Sciences from the Federal University of Ceará. Professor at the School of Medicine of the Federal University of Alagoas, University Center of Maceió and University Center CESMAC, Maceió, Alagoas, Brazil.

Cassia Fernanda Estofolete Medical Doctor, specialist in Infectology from the Hospital de Base—São José do Rio Preto. PhD in Health Sciences and Postdoctoral fellowship at the School of Medicine of São José do Rio Preto. Clinical Researcher at the Virology Laboratory at the Butantan Institute, Janssen Vaccines Prevention B.V., Medicago RD Inc, e Pfizer/BioNTech SE, Brazil.

Department of Parasitic and Infectious Diseases, School of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Sao Paulo, Brazil

Álvaro A. Faccini-Martínez Medical Doctor from Universidad Militar Nueva Granada, Bogotá, Colombia, Master in Science (emphasis on Infectious diseases) at Pontificia Universidad Javeriana, Bogotá, Colombia, and PhD in Infectious Diseases at the Universidade Federal do Espírito Santo, Brazil. Postdoctoral fellowship as International Visiting Scientist at Pathology Department, University of Texas Medical Branch, USA. Physician at the Infectious Diseases Division, Hospital Militar Central, and Services and Consulting in Infectology, Bogotá, Colombia. Cathedratic Professor at School of Medicine, Universidad Militar Nueva Granada, Bogotá, Colombia.

Gabriela Moreira Ferle Medical Doctor from the Faculty of Biomedical Sciences of Cacoal. Nephrology Residency at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brasil.

Gilberto Fontes PhD in Parasitology/Epidemiology from the Federal University of Minas Gerais. Full Professor at the Federal University of São João del Rei, Brazil. Consultant to the Pan American Health Organization (PAHO) for the Program to Eliminate Lymphatic Filariasis in the Americas. Consultant to the Ministry of Health for the Program to Eliminate Lymphatic Filariasis in Brazil and the Program to Control Geohelminthiasis in Brazil.

João Filipe Cavalcante Uchoa Furtado Medical student at the University of Fortaleza, Brazil.

Gabriela Studart Galdino Medical Doctor from the Federal University of Ceará, Residency in Internal Medicine, Master and PhD in Medical Sciences from the Federal University of Ceará, Brazil. Assistant physician and preceptor of the Internal Medicine Service of the Walter Cantídio University Hospital and Professor of the Medical School at Unichristus, Fortaleza, Ceará, Brazil.

Elodie Bomfim Hyppolito Medical Doctor, specialist in Internal Medicine from the Federal University of Ceará and Gastroenterology from the School of Medicine of Ribeirão Preto, University of São Paulo. Master in Internal Medicine from the University of São Paulo and PhD in Public Health from the Federal University of Ceará. Coordinator of Hepatitis outpatients' clinics at São José Infectious Diseases Hospital, Physician at the Liver Transplantation Division, University Hospital, Federal University of Ceará, Brazil.

Karla Cristina Petruccelli Israel Nephrologist. PhD in Tropical and Infectious Diseases from the Amazonas State University/Dr. Heitor Vieira Dourado Foundation. Collaborating Professor of the Discipline of Nephrology at the Faculty of Medicine of the Federal University of Amazonas, Brazil.

Vanderlei Carlos Bertuol Junior Medical Doctor from the University of Caxias do Sul. Nephrology residency at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil.

Gianna Mastroianni Kirsztajn Nephrologist. Master and PhD in Medicine/Nephrology and postdoctoral fellowship from the Federal University of São Paulo. Associate Professor and coordinator of the glomerulopathies sector at the Federal University of São Paulo, Brazil.

Eduardo Ribes Kohn Palacky University Olomouc, Olomouc, Czechia

Prit Kusirisin Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; Center of Excellence in Critical Care Nephrology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Izabella Picinin Safe Lacerda Infectologist. PhD from the Amazonas State University. Coordinator of HIV/AIDS Division of Amazonas State and Professor of Amazonas State University, Brazil.

Romélia Pinheiro Gonçalves Lemes Pharmacist. Master and PhD in Pharmacy/Clinical Analysis from the University of São Paulo. Full professor at the Federal University of Ceará, Brazil.

Rafael Siqueira Athayde Lima Nephrologist. Residency in Internal Medicine and Nephrology from Ribeirão Preto Medical School of the University of São Paulo, Brazil. Preceptor of medical residency at the General Hospital of Fortaleza and assistant physician at the University Hospital of the Federal University of Ceará, Brazil.

Nicole Coelho Lopes Pharmacist. Master in Pharmacology at the Federal University of Ceará, Brazil.

Gustavo Mandelli Medical Doctor. Nephrology Residency at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brasil.

Arthur Gus Manfro Medical Doctor from the Federal University of Rio Grande do Sul. Nephrology residency at the Hospital de Clínicas de Porto Alegre. PhD in Psychiatry and Behavior Sciences from the Federal University of Rio Grande do Sul, Brazil.

Alice Maria Costa Martins Pharmacist. Master's and PhD in Pharmacology from the Federal University of Ceará, Brazil. Full Professor at the Faculty of Pharmacy of the Federal University of Ceará, Brazil. Faculty member of the Postgraduate Program in Pharmacology and the Postgraduate Program in Pharmaceutical Sciences, Federal University of Ceará, Brazil.

Bruna Viana Barroso Martins Pharmacy student at the Federal University of Ceará, Brazil. Scholarship holder at the Laboratory of Pharmaceutical Bioprospecting and Clinical Biochemistry, Brazilian Research Council (CNPq).

Lisele Brasileiro Martins Pharmacist-biochemist from Universidade Paulista, specialist in Clinical Cytology, master in Tropical and Infectious Diseases from Universidade do Estado do Amazonas and PhD student in Biodiversity and Biotechnology from Universidade do Estado do Amazonas, Brazil.

Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil

Tibelle Freitas Mauricio Nurse at the Federal Institute of Education, Science and Technology of the state of Ceara, Brazil. PhD in Nursing at the Federal University of Ceara. Graduated in Nursing from the State University of Ceara and a Master in Nursing at the University of International Integration of Afro-Brazilian Lusophony (UNILAB), Brazil.

Gdayllon Cavalcante Meneses Pharmacist. Master's and PhD in Pharmacology from the Federal University of Ceará, Brazil. Postdoctoral fellow in Medical Sciences at the Federal University of Ceará, Brazil. Adjunct Professor at the Department of Clinical and Toxicological Analysis of the School of Pharmacy of the Federal University of Ceará, Brazil.

Wuelton Marcelo Monteiro Pharmacist-biochemist from the State University of Maringá, Master in Biosciences and Pathophysiology from State University of Maringá and PhD in Tropical and Infectious Diseases from the State University of Amazonas. Researcher at the Heitor Vieira Dourado Foundation for Tropical Medicine, Professor of Clinical Epidemiology at State University of Amazonas, Brazil.

Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil

Jyana Gomes Morais Nutritionist. Master's and PhD in Health Sciences from Pontifical Catholic University of Paraná, Brazil. Coordinator of the Nutrition Service and Researcher at Pró-Rim Foundation, Joinville, Santa Catarina, Brazil.

Rafaella Pessoa Moreira Associate Professor at the Institute of Health Sciences of the University of International Integration of Afro-Brazilian Lusophony (UNILAB), Brazil. Tenured professor of the Postgraduate Program in Nursing. Member of the Nursing Process Research Network (RePPE). Member of the Climate Change Task Force—NANDA-I. Postdoctorate at the University of La Laguna, Spain.

Lucio Requião Moura Nephrologist. Master and PhD in Medicine/Nephrology from the Federal University of São Paulo. Postdoctoral fellowship at the Federal University of São Paulo. Adjunct Professor at the Federal University of São Paulo, Brazil.

Saraladevi Naicker Professor Emeritus at Internal Medicine Department, University of the Witwatersrand, Johannesburg, South Africa.

Thaís Pinto Nascimento Biomedical scientist from Faculdade Estácio do Amazonas; Master in Biological Sciences from Instituto Leônidas e Maria Deane, Fiocruz Amazônia and PhD candidate in Tropical and Infectious Diseases at Universidade do Estado do Amazonas, Brazil.

Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil

Fabiana Baggio Nerbass Nutritionist. Master's degree in Nutrition from Federal University of São Paulo, Brazil. PhD and Post-doctorate in Health Sciences from Pontifical Catholic University of Paraná, Brazil. Researcher at Pró-Rim Foundation, Joinville, Santa Catarina, Brazil.

Felipe Costa Neves Nephrologist. Professor at Bahiana School of Medicine and Public Health. Supervisor of the Nephrology Residency Program at Hospital Ana Nery, Salvador, Bahia, Brazil.

Mauricio Lacerda Nogueira Medical Doctor from the Federal University of Minas Gerais, Master and PhD in Biological Sciences (Microbiology) from the Federal University of Minas Gerais, Brazil. Postdoctoral Fellowship at the National Institute of Allergy and Infectious Diseases, USA. Adjunct Professor at the School of Medicine of São José do Rio Preto, Brazil.

Department of Parasitic and Infectious Diseases, School of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Sao Paulo, Brazil

Michelle Jacintha Cavalcante Oliveira Nephrologist. PhD in Medical Sciences from the Federal University of Ceará. Adjunct Professor at the Federal University of Alagoas, Brazil.

Gabriel Sartori Pacini Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brasil

Pedro Guimarães Pascoal Medical Doctor from the Catholic University of Brasília. Nephrology residency at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil.

Edgar Sanclemente-Paz Nephrologist. Department of Internal Medicine, Faculty of Medicine, University of Cauca, Popayán, Cauca, Colombia.

Roberto Pecoits-Filho Nephrologist. PhD in Nephrology from the University of São Paulo, Brazil and held a Postdoctoral degree at the Karolinska Institute in Sweden. Senior researcher and scientific director of the Dialysis Outcomes and Practice Patterns Study (DOPPS) program at Arbor Research Collaborative for Health in Michigan, USA, and a full professor at the School of Medicine of the Pontifical Catholic University of Paraná, Brazil.

Maria Eliete Pinheiro Nephrologist. Master and PhD from the Federal University of São Paulo. Retired Full Professor of School of Medicine of the Federal University of Alagoas, Brazil. Member of the Hypertension Department of the Brazilian Society of Nephrology.

Manuela Pucca Biomedical scientist, specialist in Clinical Pathology/ Clinical Analysis, master's and doctorate in Immunology from the Faculty of Medicine of Ribeirão Preto, University of São Paulo. Assistant professor in the Department of Clinical Analysis of the Faculty of Pharmaceutical Sciences of the São Paulo State University, Brazil.

Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil

Horácio José Ramalho Nephrologist. Adjunct professor at the School of Medicine of São José do Rio Preto, Physician at the Regional School of Medicine Foundation of São José do Rio Preto, Brazil.

Division of Nephrology, Department of Internal Medicine, School of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Sao Paulo, Brazil

Rodrigo José Ramalho Nephrologist. PhD in Sciences, Nephrology program, from the School of Medicine of the University of São Paulo. Adjunct Professor of Internal Medicine at the Faculty of Medicine of São José do Rio Preto and assistant in the discipline of Nephrology at the Hospital de Base de São José do Rio Preto, Brazil.

Department of Parasitic and Infectious Diseases, School of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Sao Paulo, Brazil

Tatyana Costa Amorim Ramos Nurse graduated from the Federal University of Rondônia, Brazil. Master and PhD in Public Health from the Inter-American Faculty of Social Sciences, Paraguay. President of the Rosemary Costa Pinto Health Surveillance Foundation—Amazonas, Brazil.

Pedro Vianna Caldas Ribeiro Medical student at the University of Fortaleza, Brazil.

Marco Aurélio Sartim Pharmacist-Biochemist from the Federal University of Espírito Santo; Master and PhD in Toxicology from the Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo; Post-doctorate at the Laboratory of Toxicology of the Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo and at the Laboratory of Immunopathology of the Butantan Institute, São Paulo. Visiting Professor at the Federal University of Amazonas, Brazil.

Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil

Universidade Federal do Amazonas, Manaus, Amazonas, Brazil

Mathias Alberto Schramm Graduated in Oceanology. Master's and PhD in Food Science from the Federal University of Santa Catarina, Brazil. Professor at the Federal Institute of Education, Science and Technology of Santa Catarina, Brazil, in the Professional Master's in Climate and Environment.

Renata Asnis Schuchmann Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brasil

Carlos Ramiro Silva Ramos General Physician graduated at Universidad Mayor de San Andrés, La Paz, Bolivia. Specialist in Medical Microbiology at Pontificia Universidad Javeriana, Bogotá D.C., Colombia. Master in Biological Sciences with emphasis on Infectious Diseases at Pontificia Universidad Javeriana, Bogotá D.C., Colombia. Research and teaching assistant, as well as PhD candidate in Biological Sciences with emphasis on Infectious Diseases at Pontificia Universidad Javeriana, Bogotá D.C. Colombia.

Visith Sitprija Nephrologist. Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; Queen Saovabha Memorial Institute, Thai Red Cross, Bangkok, Thailand.

Nattachai Srisawat Nephrologist. Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; Center of Excellence in Critical Care Nephrology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; Tropical Medicine Cluster, Chulalongkorn University, Bangkok, Thailand; Academy of Science, Royal Society of Thailand, Bangkok, Thailand.

Gabriela Vieira Steckert Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brasil

Francisco Veríssimo Veronese Nephrologist. Master in Medicine/Nephrology and PhD in Medicine/Medical Sciences from the Federal University of Rio Grande do Sul, Brazil. Postdoctoral fellowship at Harvard University, Boston, USA. Past Adjunct Professor in the Department of Internal Medicine of the School of Medicine of the Federal University of Health Sciences of Porto Alegre, Brazil. Associate Professor in the Department of Internal Medicine of the School of Medicine of the Federal University of Rio Grande do Sul, Brazil.

Ariana Custódio Vieira Medical Doctor from University of the Far South Santa Catarina, Criciúma, Santa Catarina, Brazil. Nephrology residency at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil.

Marcos Alexandre Vieira Nephrologist. Master's degree in Health Sciences from Pontifical Catholic University of Paraná, Brazil. President of the Board of Trustees of the Pró-Rim Foundation, Joinville, Santa Catarina, Brazil.

Part I

The Impacts of Today's World on Tropical Diseases and Kidney Health

1 Tropical Diseases: A Public Health Problem with Impact on Nephrology

Prit Kusirisin, Visith Sitprija, and Nattachai Srisawat

1.1 Geography of the Tropics

The tropics encompass the region surrounding the equator, situated between the Tropic of Cancer at 23° 26′ 09.9″ N and the Tropic of Capricorn at 23° 26′ 09.9″ S. These latitudes align with the Earth's axial tilt, allowing the sun to be directly overhead at least once a year. This vast zone includes the northern part of Australia, most of Southeast Asia and South Asia, nearly all of Africa, and the central and southern parts of the Americas (Fig. 1.1) [1].

Currently, the tropics contain nearly 150 countries and account for 40% of the world's population. Projections suggest that by 2060, this region will accommodate approximately 60% of the global population [2]. Many countries within this area are classified by the World Bank as low- and low-middle-income countries (LLMIC), often grappling with limited access to healthcare and other essential services.

In this context, the World Health Organization (WHO) identifies a range of conditions known as "neglected tropical diseases" (NTDs) [3]. These diseases, both communicable and noncommunicable, predominantly affect populations living in poverty, lacking adequate sanitation, and exposed to infectious vectors, domestic animals, and livestock. A particularly concerning subset of NTDs is neglected zoonotic diseases (NZDs),

P. Kusirisin
Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Center of Excellence in Critical Care Nephrology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

V. Sitprija
Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Queen Saovabha Memorial Institute, Thai Red Cross, Bangkok, Thailand

N. Srisawat (✉)
Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Center of Excellence in Critical Care Nephrology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Tropical Medicine Cluster, Chulalongkorn University, Bangkok, Thailand

Academy of Science, Royal Society of Thailand, Bangkok, Thailand
e-mail: nattachai.sr@chula.ac.th

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_1

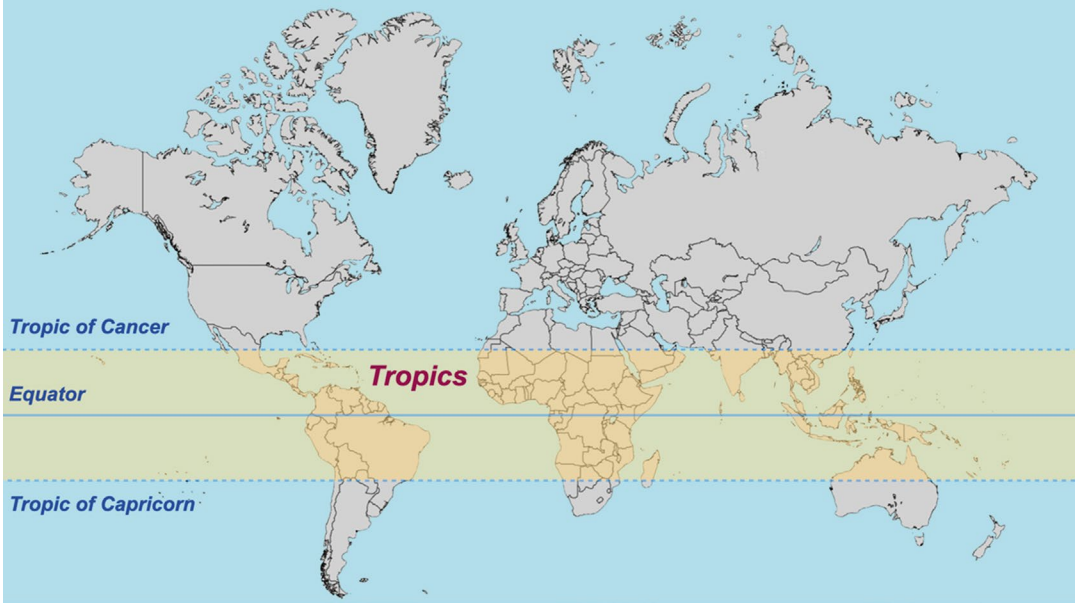


Fig. 1.1 Tropical region in the world

which pose significant health risks in tropical regions. Understanding these conditions is crucial for developing effective healthcare strategies and improving patient outcomes in these regions.

1.2 An Overview of Tropical Renal Diseases

The unique environmental conditions of tropical regions significantly contribute to various kidney-related conditions, including acute kidney injury (AKI), chronic kidney disease (CKD), electrolyte imbalances, and glomerular diseases. A global epidemiological study of AKI revealed that out of 4105 AKI cases, approximately 50% occurred in tropical regions, distributed as follows: 19% in South Asia, 14% in Latin America/Caribbean, 13% in Africa, and 4% in Oceania/Southeast Asia [4]. While dehydration accounts for nearly 50% of AKI cases worldwide, the etiology of AKI in LLMICs is more varied. These include tropical infections (45–50%), obstetric complications (15–25%), animal envenomation or the use of traditional medicines (15–20%), and surgical or post-traumatic causes (10–15%) [5, 6].

AKI in tropical regions can be broadly categorized into infectious and non-infectious causes (Table 1.1).

Common infectious causes include leptospirosis, malaria, and dengue virus. The prevalence of these infections varies geographically. For instance, leptospirosis-associated AKI is notably prevalent in the Caribbean, Central and Latin America, South Asia, Southeast Asia, and Oceania [7]. Malaria-associated AKI is highly common in Sub-Saharan Africa, South Asia, Southeast Asia, the Caribbean, and Latin America [8]. Dengue-associated AKI predominantly affects the Caribbean, Latin America, and Southeast Asia [2].

Table 1.1 Specific causes of tropical renal diseases

Infectious causes	Non-infectious causes
Bacterial infection	*Animal toxins*
Leptospirosis[a]	Snake envenomation[a]
Rickettsial disease	Arthropods
Enteric fever: salmonellosis, shigellosis	Bee, wasp, and hornet sting
Melioidosis	Caterpillars
	Spider bite
	Scorpion sting
	Jellyfish sting
	Raw carp gallbladder or bile
Viral infection	*Plant toxins*
Dengue virus[a]	Djenkol beans
Hantavirus	Starfruit
Chikungunya virus	Mushroom
	Marking nut
	Herbal medicines: impila food plants
Parasitic infection	*Chemical*
Malaria[a]	Paraquat
Filariasis	Ethylene glycol
Leishmaniasis	Ethylene dibromide
	Copper sulfate
	Chromic acid
	Formic acid
	Environment
	Natural disasters
	Heat stroke
	Miscellaneous
	Obstetric complications

[a]Common cause

1.3 Public Health Risk Dimensions Impacting Tropical Renal Diseases

Several factors contribute to the incidence of kidney diseases in tropical regions (Fig. 1.2).

1.3.1 Environmental Factors

The diverse geography and climate lead to variations in the etiology and patterns of tropical renal diseases. The tropical climate is particularly conducive to the proliferation of infectious diseases such as leptospirosis, dengue, malaria, and parasitic infections. High temperatures, humidity, and salinity facilitate the persistence of pathogens in animal reservoirs, intermediate hosts, and vectors, thereby increasing the transmission of waterborne and vector-borne diseases [9–12].

Natural disasters, including earthquakes, landslides, floods, typhoons, and tsunamis, frequently impact tropical regions [13]. Heavy rains and flooding, in particular, are strongly associated with increased cases of leptospirosis. This is also linked to occupational hazards, affecting individuals such as rice laborers, sewer workers, animal handlers, and gold miners. Soil with a pH greater than 7.0 is suspected to enhance the survival of *Leptospira* bacteria [14]. Additionally, flooding can raise the incidence of snakebites as snakes are displaced from their burrows into areas frequented by humans, especially farmers and field workers [15, 16].

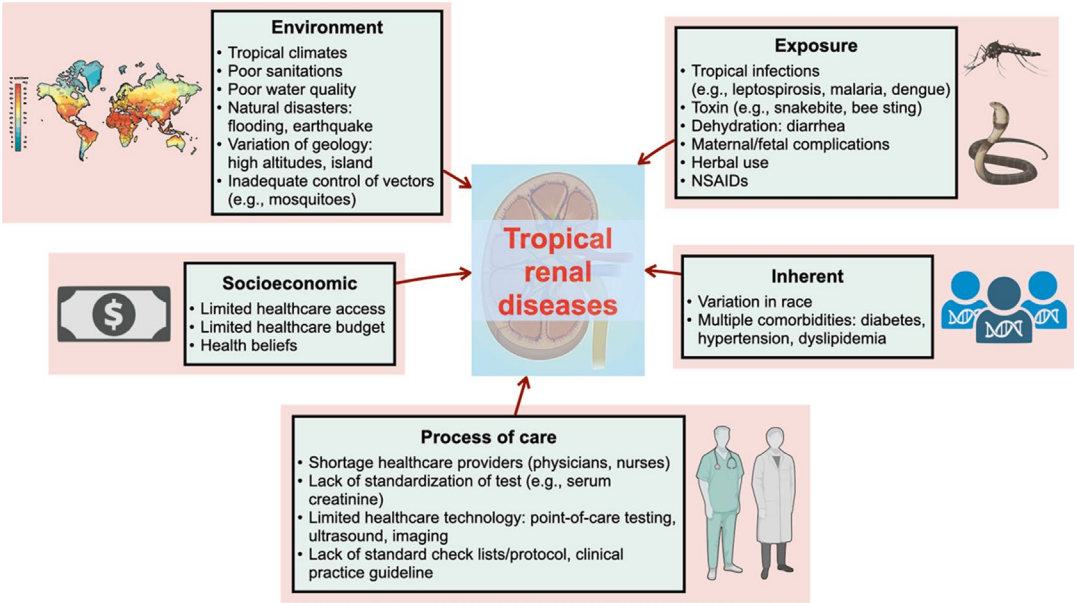


Fig. 1.2 Public health impact of tropical renal diseases. **Abbreviation**: *NSAIDs* non-steroidal anti-inflammatory drugs

Earthquakes contribute to kidney disease through complications such as crush syndrome, which results in rhabdomyolysis due to prolonged entrapment under debris [17]. This condition can lead to hypovolemic shock, acute oliguric AKI, hyperkalemia, and metabolic acidosis, with mortality rates for dialyzed patients ranging from 15% to 40% [18–20]. Furthermore, traumatic bleeding from earthquakes can result in hypovolemic shock, pre-renal AKI, and, subsequently, acute tubular necrosis (ATN). Nephrotoxic drugs contribute to approximately one-third of trauma-related AKI cases, and penetrating trauma to the urinary tract system can lead to post-renal AKI. Effective management of earthquake-associated AKI includes early and adequate fluid resuscitation with potassium-sparing fluids to manage hyperkalemia [21, 22].

The soil in tropical regions, often degraded by high temperatures and heavy rainfall, can leach minerals and organic compounds into water sources, leading to contamination and waterlogging of agricultural fields. This contamination, particularly with heavy metals, is associated with CKD of unknown etiology (CKDu). CKDu, characterized by CKD without traditional risk factors such as diabetes, hypertension, or human immunodeficiency virus (HIV), is increasingly reported in regions including Central America, East Asia, and South Asia [23–26].

Heat stress, a condition prevalent in hot environments during summer months, poses a significant risk for AKI and CKD, particularly during prolonged heat waves [2, 27–29]. The primary risk factor for heat-related nephropathy is dehydration, commonly encountered among individuals in high-risk occupations such as agriculture, construction, firefighting, and mining [27]. Recurrent dehydration can trigger the polyol-fructokinase and vasopressin pathways due to elevated serum osmolality, while heat stress combined with strenuous physical exertion can lead to rhabdomyolysis and elevated uric acid levels [30–33]. Although the precise mechanisms by which heat stress contributes to CKD remain unclear, the interplay between dehydration, heat exposure, physical labor, and unidentified toxins may elucidate the prevalence of CKDu observed in Asia and Latin America [34, 35].

1.3.2 Socioeconomic Factors

The socioeconomic landscape of tropical regions is marked by significant heterogeneity, which influences the prevalence and patterns of kidney diseases. Compared to temperate climates, tropical populations exhibit a broader range of socioeconomic statuses, lifestyles, education levels, and access to goods, services, and medical care. In resource-sufficient settings within the tropics, kidney disease patterns often resemble those observed in high-income countries. Affected individuals in these settings are typically older and may have comorbid chronic conditions or complications from postsurgical procedures, making them more susceptible to hospital-acquired AKI. Additionally, countries in tropical regions generally have lower gross domestic product (GDP) per capita than those in higher latitudes, with lower GDP correlating with higher rates of community-acquired AKI [36, 37].

Conversely, in resource-limited settings such as parts of South Asia and Southeast Asia, tropical renal diseases are primarily community-acquired and predominantly affect younger, otherwise healthy individuals. Rural populations in these areas face significant environmental health risks, including malnutrition and limited access to standard healthcare, which contribute to a higher incidence of AKI. For example, maternal malnutrition can lead to low birth weight and reduced nephron counts in children, predisposing them to impaired immunity, hypertension, cardiovascular disease, and kidney disease later in life [13].

In urban areas, large slum populations often face conditions akin to those in rural regions, with severely restricted access to basic amenities. The convergence of poverty, lack of access to potable water, inadequate sanitation, substandard housing, and insufficient regulatory oversight increases the risk of exposure to industrial toxins that can cause AKI [13].

1.3.3 Process of Care Factors: Shortage of Nephrologists in the Tropics

Despite the vast population and geographic diversity of the tropics, significant disparities exist in economic prosperity and healthcare infrastructure across these countries. One of the most critical challenges is the severe shortage of healthcare professionals, particularly internists and nephrologists [38]. The scarcity of nephrologists is exacerbated by outdated and incomplete registries; available data show a wide variation in the number of nephrologists per million population (pmp), ranging from as low as 0.2 pmp to as high as 79 pmp [39–41].

The distribution of nephrologists within tropical countries is also highly uneven, with the majority located in capital cities or major regional hospitals. For example, Bangkok has approximately 25 nephrologists pmp, whereas regional areas of Thailand average only 12 pmp. This concentration of nephrologists in urban centers creates significant barriers to the effective management of kidney diseases in more remote areas. The shortage is further compounded by the heavy workloads of internists and general practitioners, who often manage kidney disease without specialized training. This situation often results in delays in diagnosis and treatment, with patients facing extended waits before referral to nephrologists for specialized care (Fig. 1.3).

Additionally, the emigration of nephrologists to higher-income countries, including the United States, exacerbates the shortage in some regions, particularly in parts of Africa [42, 43].

To address these disparities, targeted efforts are needed to improve the distribution of nephrologists and enhance the capacity of general practitioners to recognize and manage renal conditions effectively. Developing and implementing strategies for training and deploying nephrologists in underserved areas could substantially improve the care of patients with tropical renal diseases.

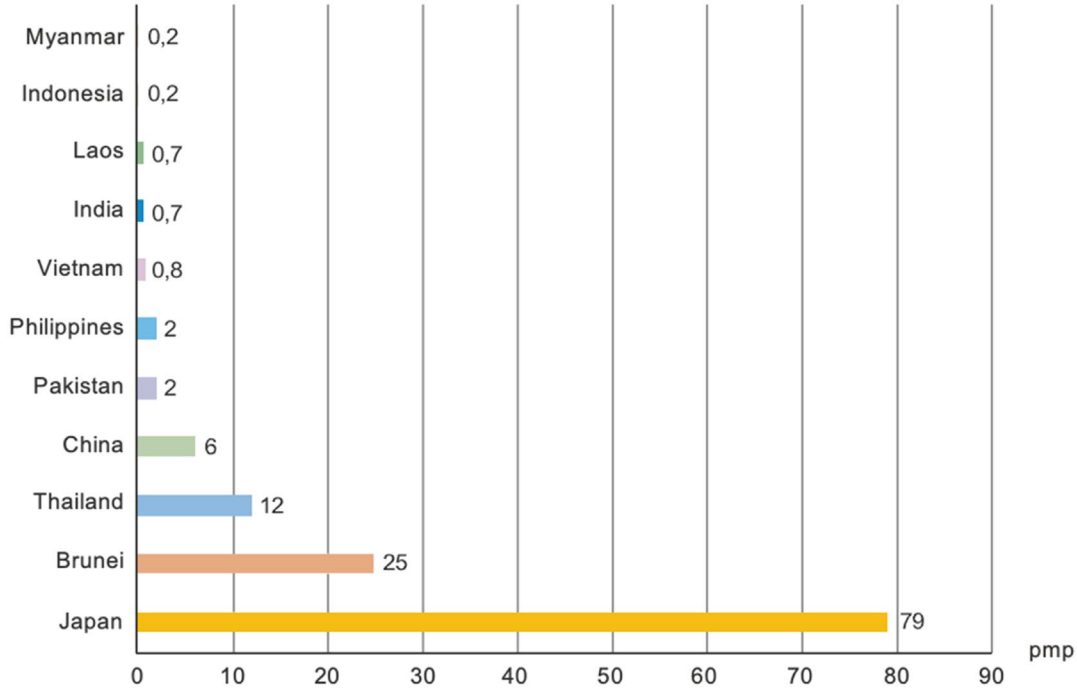


Fig. 1.3 Distribution of nephrologists in Asian countries

1.3.4 Exposure Factors

Tropical infections are a significant cause of kidney diseases in tropical regions, representing major community-acquired renal emergencies. These infections, which can lead to AKI, are primarily caused by viruses, bacteria, and parasites. Prominent pathogens include leptospirosis, malaria, and dengue virus [2].

Leptospirosis is a notable zoonosis prevalent in tropical areas, although it has also been reported sporadically in developed countries due to global travel. This infection can lead to Weil's syndrome, a severe condition characterized by AKI and hyperbilirubinemia. The incidence of AKI in leptospirosis can reach up to 84%, approximately double the incidence observed in intensive care units [44]. Kidney injury in leptospirosis results from both direct bacterial effects and indirect factors such as dehydration, rhabdomyolysis, and bleeding [45, 46].

Malaria is endemic in tropical and subtropical regions and is caused by five *Plasmodium* species: *P. vivax*, *P. falciparum*, *P. malariae*, *P. ovale*, and *P. knowlesi* [47]. Over the past 15 years, the global burden of malaria has decreased, with malaria cases dropping from 262 million in 2000 to 214 million in 2015 (approximately a 20% reduction) and deaths decreasing from 839,000 to 438,000 (about 50%) [8]. The incidence of malaria-associated AKI varies widely, from 0.5% to 30%, depending on patient demographics and AKI diagnostic criteria [1, 47–50]. In 2015, the majority of malaria-related deaths occurred in Africa (90%), followed by Southeast Asia (7%) and the Eastern Mediterranean (2%) [8].

Dengue fever is another major tropical disease, affecting approximately one-third of the global population, with an estimated annual infection rate of 50–100 million cases [51]. Dengue infection can result in a range of renal conditions, including pre-renal AKI, ATN due to both direct and indirect effects, thrombotic microangiopathy, glomerulopathy (including IgG, C3, and IgM deposition), and proliferative glomerulonephritis [52]. The prevalence of dengue-associated AKI varies from 0.2% to

35.7%, influenced by variations in AKI definitions, age groups, and the severity of dengue infection [53–56].

Fluid and electrolyte disorders are frequently observed in patients with tropical infections. These include hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, hyperphosphatemia, and hypomagnesemia [57]. For example, 75% of leptospirosis patients exhibit hypermagnesiuria, and 50% demonstrate decreased phosphate reabsorption thresholds, although these abnormalities usually resolve within 2 weeks of treatment [58].

Non-infectious exposures also play a significant role in AKI in the tropics. These include snakebites, plant toxins, and chemical toxins [2].

- *Snakebite* is a major contributor, accounting for 70% of community-acquired AKI in Myanmar, 2–3% in India, and 1–2% in Thailand [59]. The incidence of snakebite-associated AKI ranges from 1.4% to 38%, with mortality rates between 1% and 20%, depending on the snake species [60, 61]. Kidney injury typically occurs within hours of the bite but can also develop days later. Mechanisms of injury include direct and indirect effects, such as dehydration, hemolysis, rhabdomyolysis, and disseminated intravascular coagulation (DIC). Common AKI patterns include ATN, acute interstitial nephritis, and acute cortical necrosis, with occasional cases of necrotizing and crescentic glomerulonephritis. More than 90% of patients develop oliguria and may require dialysis [60]. Early administration of specific antivenom and timely dialysis are critical for managing snakebite-associated AKI.
- *Wasp and bee stings* are also significant causes of AKI, especially in South Asia and Latin America. Africanized bees, in particular, have caused numerous cases since the 1950s [62]. Recent data from China indicate that the severity of wasp stings is correlated with the number of stings, with severe systemic symptoms, including kidney and liver injury, occurring with approximately ten or more stings [63].
- *Raw carp bile* (fish gallbladder) is used in rural areas of Southeast Asia for treating acne, improving visual efficiency, and relieving arthritis. Its toxicity, known as ichthyotoxicity, is due to sodium cyprinol sulfate, a heat-stable bile acid. This toxin remains potent even after cooking, leading to acute liver failure and oliguric AKI [64].
- *Tropical plant toxins* that cause AKI include djenkol beans in Thailand, impila (*Callilepis laureola*), starfruit (*Averrhoa carambola*), poisonous mushrooms (*Amanita phalloides*), cottonseed oil (gossypol) in China that causes hypokalemia and distal renal tubular acidosis, and Chinese herbs containing aristolochic acid, which induces tubular atrophy and interstitial fibrosis [65–71]. These toxins illustrate the intersection of cultural practices, traditional medicine, and environmental factors in tropical regions.
- *Chemical intoxication*, often due to inadequate occupational protective measures, is a significant risk factor for AKI in tropical regions. Exposure to toxic substances such as paraquat, copper sulfate, ethylene dibromide, and ethylene glycol can cause severe kidney damage. Paraquat, a potent herbicide, induces oxidative stress and cellular apoptosis, with clinical manifestations ranging from gastrointestinal irritation to rapid multi-organ failure, depending on the dose ingested [72, 73]. Despite its severe toxicity, no antidote exists for paraquat poisoning, necessitating hospitalization and supportive care to manage complications [72, 74]. Similarly, ethylene glycol, found in antifreeze and certain medicinal products, leads to AKI through the formation of calcium oxalate crystals that damage renal tubules [75, 76].
- *Obstetric complications* are also a notable cause of AKI in Asia. Studies from India indicate that AKI occurs in 0.06–2% of delivery cases, with placental abruption, pre-eclampsia, and puerperal sepsis being the most common causes of pregnancy-related AKI [77, 78].

These complications underscore the impact of limited access to quality healthcare services.

1.3.5 Inherent Factors

Inherent factors contributing to AKI include age, gender, genetic susceptibility, and comorbid conditions such as diabetes mellitus, hypertension, malignancy, and pre-existing CKD [38]. Historically, these factors may have been less impactful on AKI compared to other determinants, particularly in comparison to developed countries. However, with increasing urbanization and globalization, the influence of inherent factors on the incidence of AKI in tropical regions has become more significant.

Age and Gender Age and gender are pivotal inherent factors influencing AKI. Elderly individuals are generally at higher risk due to decreased renal reserve and the presence of multiple comorbid conditions. Gender disparities in AKI prevalence and outcomes are influenced by various biological and social factors [79].

Genetic Susceptibility Genetic predispositions are crucial in determining susceptibility to AKI. In tropical regions, certain genetic disorders are more prevalent and can exacerbate the risk of AKI. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is common in tropical populations, increases the risk of intravascular hemolysis and subsequent kidney injury [80]. Additionally, mutations in the human anion exchanger 1 (AE1) of the basolateral membrane of α-intercalated cells in the renal collecting duct are associated with distal renal tubular acidosis and renal stone formation, a condition notably observed in Southeast Asia and referred to as Southeast Asian ovalocytosis [81].

Comorbid Conditions Comorbidities such as diabetes mellitus, hypertension, and pre-existing CKD substantially impact the risk of AKI. These conditions contribute to the progression of kidney damage and enhance the kidney's vulnerability to acute insults. Furthermore, adverse events from treatments, including renin-angiotensin-aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors, can exacerbate renal impairment. Malignancies complicate the clinical scenario further, with disease-related factors or treatment-related issues, such as surgery, chemotherapy, or radiation, increasing the risk of AKI.

Inflammatory and Autoimmune Diseases Inflammatory and autoimmune diseases prevalent in tropical regions also contribute to AKI. Takayasu arteritis, characterized by inflammation of the aorta and its major branches, is commonly observed in South Asia and Southeast Asia. This condition can involve the renal arteries, leading to secondary kidney injury and exacerbating AKI, or accelerating the progression of CKD [82–84].

1.4 Tropical Renal Diseases and the "One Health" Approach

In developing countries, community-acquired AKI is predominantly driven by tropical infectious diseases, contrasting with the hospital-acquired AKI more common in developed countries [85]. Addressing tropical infection-related AKI necessitates effective prevention and control strategies, and the "One Health" approach offers a comprehensive framework for tackling this challenge.

The "One Health" approach integrates human, animal (reservoir), and environmental health considerations to predict and control diseases at the interface of humans-animals-ecosystems. This holistic perspective enhances disease prediction and management by acknowledging the interconnectedness of these three components [86]. By promoting collaborative, inter-sectoral, and multidisciplinary strategies, the "One Health" approach aims to improve overall disease control and prevention.

Leptospirosis and malaria, two prominent tropical infections associated with AKI, serve as exemplary models for the "One Health" approach.

Leptospirosis is strongly linked to environmental factors such as heavy rains and flooding, which facilitate the survival and spread of the causative bacteria in neutral soil and alkaline water. This disease predominantly affects individuals in high-risk occupational groups, including rice laborers, sewer workers, animal handlers, and gold miners. Understanding these environmental and occupational risk factors is crucial for targeting and implementing effective interventions [14, 86].

Malaria transmission occurs primarily through mosquito bites, with several factors influencing its prevalence. Systematic reviews reveal that climate change, insufficient preventive measures (such as bed nets and repellents), poor infrastructure, limited healthcare resources, and issues with drug efficacy and adherence significantly contribute to malaria transmission [13, 87]. An integrated health strategy that addresses these factors is essential for mitigating the impact of malaria on renal health.

Socioeconomic conditions profoundly affect the prevalence of tropical infections leading to AKI. Urban or peri-urban areas with inadequate waste management and sanitation are often hotspots for these infections. Factors such as poverty, limited access to clean drinking water, insufficient sanitation services, and substandard housing conditions exacerbate the risk of infection and subsequent kidney injury [59]. Addressing these socioeconomic determinants is vital for reducing the incidence of infection-related AKI.

To effectively combat zoonosis diseases, it is imperative to address gaps in scientific and technological knowledge that delay case detection and hinder surveillance efforts. While vaccines are a crucial tool for controlling tropical infections, their availability remains limited. Developing and deploying effective vaccines is essential for reducing the incidence and impact of these diseases.

In summary, adopting a "One Health" approach to managing tropical renal diseases involves a comprehensive strategy that integrates human, animal, and environmental health factors. Improving understanding of these interconnections, addressing socioeconomic drivers, and advancing research in vaccination efforts can enhance the ability to prevent and manage tropical infection-related AKI.

1.5 Strategies to Improve AKI Recognition in the Tropics

1.5.1 Risk Assessment and Use of Clinical Risk Scores

Accurate recognition of AKI in tropical regions requires understanding of both general and region-specific risk factors. Common risk factors for AKI include advanced age, heart failure, liver failure, CKD, anemia, and exposure to nephrotoxic agents. Additionally, infections, sepsis, shock, mechanical ventilation, and surgery are recognized as high-risk settings for AKI development [88, 89].

Community-acquired AKI presents distinct risk factors compared to hospital-acquired AKI. For instance, in the Southeast Asia-AKI (SEA-AKI) study, risk factors for community-acquired AKI include female gender, obesity, diabetes, and the APACHE II score. Conversely, hospital-acquired AKI is primarily associated with obesity, the APACHE II score, and the duration of observation [90].

To facilitate early diagnosis of leptospirosis in rural areas, the THAI-LEPTO score has been proposed. This score, based on clinical parameters and simple laboratory tests, integrates seven variables with specific odds ratios: hypotension (3), jaundice (2), muscle pain (2), AKI (1.5), low hemoglobin (3), hypokalemia with hyponatremia (3), and neutrophilia (1). The THAI-LEPTO score demonstrates high discriminatory power with an area under the curve (AUC) of 0.82 (95% CI 0.67 ± 0.97) on fever days 3 and 4 [91]. Additionally, the outpatient department (OPD) score, used in outpatient settings, includes factors such as history of exposure to wet ground at the workplace, contact with water reservoirs used by animals, positive urine dipstick tests for protein and blood, and an elevated neutrophil count >80%, with an AUC of 0.72 [92].

In the context of malaria, risk factors for AKI include age, absence of fever, elevated heart rate, reduced diastolic blood pressure, icterus, hepatomegaly, and elevated direct bilirubin levels [93].

For dengue patients, factors such as dengue hemorrhagic fever, rhabdomyolysis, multiple-organ dysfunction, diabetes mellitus, delayed hospitalization, and the use of nephrotoxic drugs are associated with an increased risk of AKI [94].

Research on snakebite patients in Myanmar identifies several independent risk factors for AKI, including bites from Viperidae species, white blood cell counts $>10 \times 10^3$ cells/μL, overt DIC, serum creatinine kinase levels >500 IU/L, serum sodium levels <135 mmol/L, microscopic hematuria, and a delay of ≥2 h from the snakebite to antivenom treatment [95].

Clinical risk scores are crucial for predicting AKI development. Established scores such as the AKI following cardiac surgery (AKICS) scores and the Mehran scores are well-recognized for assessing risk in cardiac surgery and contrast exposure, respectively. The renal angina index, which stratifies patients into moderate-, high-, and very high-risk categories based on changes in serum creatinine and the duration of oliguria, has demonstrated superior performance in predicting severe AKI compared to KDIGO criteria [96].

Despite these advancements, there is a pressing need for risk scores tailored specifically to tropical disease-related AKI.

1.5.2 Novel Biomarkers for AKI in Tropical Renal Diseases

Novel biomarkers hold promise for improving the early diagnosis of AKI associated with tropical diseases. For leptospirosis-associated AKI, urinary and plasma neutrophil gelatinase-associated lipocalin (NGAL) have proven valuable, with AUCs of 0.91 and 0.92, respectively [97]. Serum kidney injury molecule-1 (KIM-1) also shows promise, with an AUC of 0.86 [98]. Other biomarkers include endothelial injury markers such as intercellular adhesion molecule-1 (ICAM-1) and syndecan-1 [99]. Differences in microRNA profiles, including serum miR155-5p and miR630, may differentiate severe from non-severe leptospirosis [100]. Although diagnostic tests recommended by the WHO, such as the microscopic agglutination test, direct culture, and polymerase chain reaction (PCR) techniques, are highly specific, they require advanced facilities that are not universally available [101]. Rapid diagnostic tests, such as the serum IgM antibody test, have lower sensitivity, particularly in the early stages of illness [101]. Recent advances in RPA-CRISPR/Cas12 targeting the LipL32 gene offer promising results with acceptable sensitivity and excellent specificity for detecting leptospires [102].

In the case of snakebite, early biomarkers are needed for the diagnosis and treatment of snakebite-associated AKI. The elevation in urinary NGAL and clusterin along with serum cystatin C can predict AKI development following Russell viper bites [103]. Urinary KIM-1 in mice has been found elevated within 24 hours of envenomation before the rise of creatinine or any pathological changes in renal tissue [104].

1.5.3 Increased Recognition of AKI by Electronic Alerts and Telemedicine

The integration of electronic health systems for monitoring and reporting creatinine levels has become a standard practice in many hospitals. Since the introduction of electronic alerts (e-alerts) in 1994, these systems have been instrumental in improving the early detection of AKI [105]. E-alerts are associated with increased AKI detection by prompting physicians to consider this diagnosis more frequently and reducing the likelihood of missed cases, particularly in settings where healthcare providers are overburdened. By incorporating e-alerts into electronic health records, healthcare systems can better organize AKI data, which can be coded using ICD-10 classifications. Accurate reporting of AKI incidence through these systems contributes to national registries and provides valuable insights into the overall burden of AKI in tropical regions.

Despite their potential benefits, the clinical impact of e-alerts has been variable. For instance, some studies have found no significant improvement in clinical outcomes following the implementation of e-alerts for AKI in a hospital-wide setting [106]. This lack of outcome improvement may be due to the absence of changes in clinical management triggered by the alerts. Conversely, other research has shown that AKI alerts lead to more timely and effective interventions and a trend toward reduced progression of AKI [107]. While e-alerts have not consistently demonstrated improvements in mortality rates, they can alleviate physician workload and shorten the time between AKI diagnosis and nephrologist consultation [108].

Telemedicine offers a valuable tool for enhancing AKI management, especially in community hospitals. Through web-based conferences, group messaging, or telephone consultations, physicians in these settings can directly obtain guidance from nephrologists.

To improve the diagnostic accuracy and management of AKI in tropical settings, it is recommended to adopt a streamlined approach that incorporates clinical risk scores, point-of-care tests, and biomarkers alongside AKI e-alerts. Physicians should adhere to established AKI care bundles, which include:

- Withholding nephrotoxic agents
- Discontinuing RAAS inhibitors
- Optimizing fluid balance
- Avoiding hyperglycemia
- Considering alternatives to radiocontrast agents
- Monitoring serum creatinine and urine output closely

Implementing these care bundles, coupled with timely consultation with nephrologists via telemedicine, can help avert the progression of AKI in some patients. For those with severe AKI requiring kidney replacement therapy, telemedicine also facilitates the consideration of nephrologists being promptly referred to provincial hospitals as needed (Fig. 1.4).

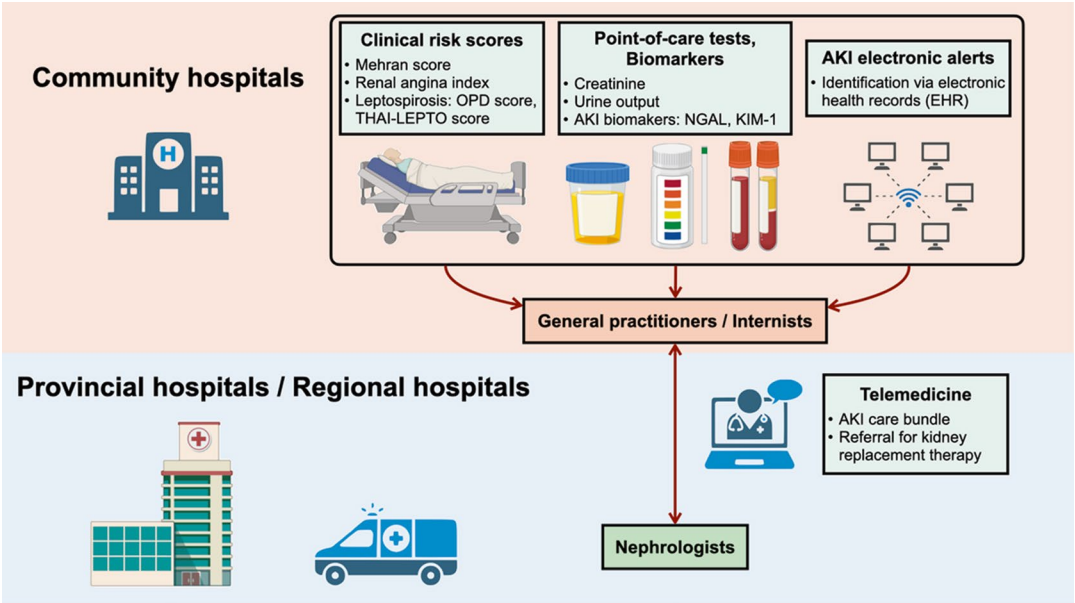


Fig. 1.4 Network connecting general practitioners and nephrologists in the context of community and referral hospitals using telemedicine. **Abbreviation**: *AKI* acute kidney injury

1.6 Conclusion

Reflecting on Sir Michael Marmot's insight that "all matters are health matters" and the WHO's definition of health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity," it is evident that enhancing renal disease outcomes in the tropics demands a comprehensive approach. This approach must consider five critical components: environmental factors, socioeconomic conditions, processes of care, exposure factors, and inherent patient characteristics. Each of these elements exhibits unique features and variations across different regions of the world. The specific challenges in tropical regions, such as limited transportation infrastructure, constrained healthcare budgets, a shortage of nephrologists, and the prevalence of endemic infections contributing to AKI, highlight the complexity of improving kidney disease management. To address these challenges effectively, strategies should include the widespread implementation of educational programs on AKI risk scores and the integration of telemedicine in primary healthcare settings. By focusing on these areas, significant advancements can be made in the recognition, management, and overall quality of life for individuals suffering from renal diseases in tropical regions.

References

1. Burdmann EA, Jha V. Acute kidney injury due to tropical infectious diseases and animal venoms: a tale of 2 continents. Kidney Int. 2017;91(5):1033–46.
2. Kusirisin P, da Silva Junior GB, Sitprija V, Srisawat N. Acute kidney injury in the tropics. Nephrology (Carlton). 2023;28(1):5–20.
3. Silva Junior G, Srisawat N, Sirivongrangson P, Fayad T, Sanclemente E, Daher E. Neglected tropical diseases and the kidneys. Contrib Nephrol. 2021;199:201–28.
4. Mehta RL, Burdmann EA, Cerda J, Feehally J, Finkelstein F, Garcia-Garcia G, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 global snapshot: a multinational cross-sectional study. Lancet. 2016;387(10032):2017–25.
5. Daher Ede F, Junior Silva GB, Vieira AP, Souza JB, Falcao Fdos S, Costa CR, et al. Acute kidney injury in a tropical country: a cohort study of 253 patients in an infectious diseases intensive care unit. Rev Soc Bras Med Trop. 2014;47(1):86–9.
6. Barsoum RS. Tropical acute renal failure. Contrib Nephrol. 2004;144:44–52.
7. Pappas G, Papadimitriou P, Siozopoulou V, Christou L, Akritidis N. The globalization of leptospirosis: worldwide incidence trends. Int J Infect Dis. 2008;12(4):351–7.
8. Severe falciparum malaria. World Health Organization, communicable diseases cluster. Trans R Soc Trop Med Hyg. 2000;94(Suppl 1):S1–90.
9. Santos IOC, Landi MFA, Cruz LM, Bofill MIR, Santos DED, Lima EMM, et al. Human leptospirosis in the Federal District, Brazil, 2011–2015: eco-epidemiological characterization. Rev Soc Bras Med Trop. 2017;50(6):777–82.
10. Gomes AF, Nobre AA, Cruz OG. Temporal analysis of the relationship between dengue and meteorological variables in the city of Rio de Janeiro, Brazil, 2001–2009. Cad Saude Publica. 2012;28(11):2189–97.
11. Githeko AK, Ototo EN, Guiyun Y. Progress towards understanding the ecology and epidemiology of malaria in the western Kenya highlands: opportunities and challenges for control under climate change risk. Acta Trop. 2012;121(1):19–25.
12. Haque U, Hashizume M, Glass GE, Dewan AM, Overgaard HJ, Yamamoto T. The role of climate variability in the spread of malaria in Bangladeshi highlands. PLoS One. 2010;5(12):e14341.
13. Jha V, Parameswaran S. Community-acquired acute kidney injury in tropical countries. Nat Rev Nephrol. 2013;9(5):278–90.
14. Schneider MC, Najera P, Pereira MM, Machado G, dos Anjos CB, Rodrigues RO, et al. Leptospirosis in Rio Grande do Sul, Brazil: an ecosystem approach in the animal-human interface. PLoS Negl Trop Dis. 2015;9(11):e0004095.
15. Rodrigues Sgrignolli L, Florido Mendes GE, Carlos CP, Burdmann EA. Acute kidney injury caused by bothrops snake venom. Nephron Clin Pract. 2011;119(2):c131–6; discussion c7.
16. Chugh KS. Snake-bite-induced acute renal failure in India. Kidney Int. 1989;35(3):891–907.
17. Sheng ZY. Medical support in the Tangshan earthquake: a review of the management of mass casualties and certain major injuries. J Trauma. 1987;27(10):1130–5.
18. Oda J, Tanaka H, Yoshioka T, Iwai A, Yamamura H, Ishikawa K, et al. Analysis of 372 patients with crush syndrome caused by the Hanshin-Awaji earthquake. J Trauma. 1997;42(3):470–5; discussion 5–6.
19. He Q, Wang F, Li G, Chen X, Liao C, Zou Y, et al. Crush syndrome and acute kidney injury in the Wenchuan earthquake. J Trauma. 2011;70(5):1213–7; discussion 7–8.
20. Hatamizadeh P, Najafi I, Vanholder R, Rashid-Farokhi F, Sanadgol H, Seyrafian S, et al. Epidemiologic aspects of the Bam earthquake in

Iran: the nephrologic perspective. Am J Kidney Dis. 2006;47(3):428–38.
21. Sever MS, Vanholder R, the RDRTF of ISN Work Group on Recommendations for the Management of Crush Victims in Mass Disasters. Recommendation for the management of crush victims in mass disasters. Nephrol Dial Transplant. 2012;27(Suppl 1):i1–67.
22. Sever MS, Lameire N, Van Biesen W, Vanholder R. Disaster nephrology: a new concept for an old problem. Clin Kidney J. 2015;8(3):300–9.
23. Martin-Cleary C, Ortiz A. CKD hotspots around the world: where, why and what the lessons are. A CKJ review series. Clin Kidney J. 2014;7(6):519–23.
24. Correa-Rotter R, Wesseling C, Johnson RJ. CKD of unknown origin in Central America: the case for a Mesoamerican nephropathy. Am J Kidney Dis. 2014;63(3):506–20.
25. Tsai CC, Wu CL, Kor CT, Lian IB, Chang CH, Chang TH, et al. Prospective associations between environmental heavy metal exposure and renal outcomes in adults with chronic kidney disease. Nephrology (Carlton). 2018;23(9):830–6.
26. Wijewickrama E, Behera S, Garcia P, Avila-Casado C, Caplin B, Paolo VS, et al. Kidney biopsies among persons living in hotspots of CKDu: a position statement from the International Society of Nephrology's consortium of collaborators on CKDu. Kidney Int. 2024;105(3):464–9.
27. Nerbass FB, Pecoits-Filho R, Clark WF, Sontrop JM, McIntyre CW, Moist L. Occupational heat stress and kidney health: from farms to factories. Kidney Int Rep. 2017;2(6):998–1008.
28. Glaser J, Lemery J, Rajagopalan B, Diaz HF, Garcia-Trabanino R, Taduri G, et al. Climate change and the emergent epidemic of CKD from heat stress in rural communities: the case for heat stress nephropathy. Clin J Am Soc Nephrol. 2016;11(8):1472–83.
29. Borg M, Bi P, Nitschke M, Williams S, McDonald S. The impact of daily temperature on renal disease incidence: an ecological study. Environ Health. 2017;16(1):114.
30. Madero M, Garcia-Arroyo FE, Sanchez-Lozada LG. Pathophysiologic insight into MesoAmerican nephropathy. Curr Opin Nephrol Hypertens. 2017;26(4):296–302.
31. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5):442–8.
32. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int. 2011;79(12):1361–9.
33. Sanchez-Lozada LG, Garcia-Arroyo FE, Gonzaga G, Silverio O, Blas-Marron MG, Munoz-Jimenez I, et al. Kidney injury from recurrent heat stress and rhabdomyolysis: protective role of allopurinol and sodium bicarbonate. Am J Nephrol. 2018;48(5):339–48.
34. Herath C, Jayasumana C, De Silva P, De Silva PHC, Siribaddana S, De Broe ME. Kidney diseases in agricultural communities: a case against heat-stress nephropathy. Kidney Int Rep. 2018;3(2):271–80.
35. Redmon JH, Levine KE, Lebov J, Harrington J, Kondash AJ. A comparative review: chronic kidney disease of unknown etiology (CKDu) research conducted in Latin America versus Asia. Environ Res. 2021;192:110270.
36. Schieppati A, Perico N, Remuzzi G. Eliminating treatable deaths due to acute kidney injury in resource-poor settings. Semin Dial. 2015;28(2):193–7.
37. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, et al. Acute kidney injury: an increasing global concern. Lancet. 2013;382(9887):170–9.
38. Lewington AJ, Cerda J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. Kidney Int. 2013;84(3):457–67.
39. Fukuhara S, Yamazaki C, Hayashino Y, Higashi T, Eichleay MA, Akiba T, et al. The organization and financing of end-stage renal disease treatment in Japan. Int J Health Care Finance Econ. 2007;7(2–3):217–31.
40. Liu ZH. Nephrology in China. Nat Rev Nephrol. 2013;9(9):523–8.
41. Neilson EG, Hull AR, Wish JB, Neylan JF, Sherman D, Suki WN. The ad hoc committee report on estimating the future workforce and training requirements for nephrology. The Ad Hoc committee on nephrology manpower needs. J Am Soc Nephrol. 1997;8(5 Suppl 9):S1–4.
42. Gharbi MB. Renal replacement therapies for end-stage renal disease in North Africa. Clin Nephrol. 2010;74:S17–S9.
43. Kusirisin P, Srisawat N. Hemodiafiltration in developing countries. Semin Dial. 2022;35(5):449–56.
44. Silva Junior GB, Abreu KL, Mota RM, Barreto AG, Araujo SM, Rocha HA, et al. RIFLE and acute kidney injury network classifications predict mortality in leptospirosis-associated acute kidney injury. Nephrology (Carlton). 2011;16(3):269–76.
45. Sitprija V. Renal involvement in human leptospirosis. Br Med J. 1968;2(5606):656–8.
46. Daher Ede F, de Abreu KL, da Silva Junior GB. Leptospirosis-associated acute kidney injury. J Bras Nefrol. 2010;32(4):400–7.
47. Silva GBDJ, Pinto JR, Barros EJG, Farias GMN, Daher EF. Kidney involvement in malaria: an update. Rev Inst Med Trop Sao Paulo. 2017;59:e53.
48. Sitprija V, Vongsthongsri M, Poshyachinda V, Arthachinta S. Renal failure in malaria: a pathophysiologic study. Nephron. 1977;18(5):277–87.
49. Kute VB, Trivedi HL, Vanikar AV, Shah PR, Gumber MR, Patel HV, et al. Plasmodium vivax malaria-associated acute kidney injury, India, 2010-2011. Emerg Infect Dis. 2012;18(5):842–5.
50. Sitprija V, Indraprasit S, Pochanugool C, Benyajati C, Piyaratn P. Renal failure in malaria. Lancet. 1967;1(7483):185–8.

51. Malavige GN, Fernando S, Fernando DJ, Seneviratne SL. Dengue viral infections. Postgrad Med J. 2004;80(948):588–601.
52. Lizarraga KJ, Nayer A. Dengue-associated kidney disease. J Nephropathol. 2014;3(2):57–62.
53. Laoprasopwattana K, Pruekprasert P, Dissaneewate P, Geater A, Vachvanichsanong P. Outcome of dengue hemorrhagic fever-caused acute kidney injury in Thai children. J Pediatr. 2010;157(2):303–9.
54. Lee IK, Liu JW, Yang KD. Clinical characteristics, risk factors, and outcomes in adults experiencing dengue hemorrhagic fever complicated with acute renal failure. Am J Trop Med Hyg. 2009;80(4):651–5.
55. Khan NA, Azhar EI, El-Fiky S, Madani HH, Abuljadial MA, Ashshi AM, et al. Clinical profile and outcome of hospitalized patients during first outbreak of dengue in Makkah, Saudi Arabia. Acta Trop. 2008;105(1):39–44.
56. Basu G, Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, et al. Acute kidney injury in tropical acute febrile illness in a tertiary care centre–RIFLE criteria validation. Nephrol Dial Transplant. 2011;26(2):524–31.
57. Sitprija V. Altered fluid, electrolyte and mineral status in tropical disease, with an emphasis on malaria and leptospirosis. Nat Clin Pract Nephrol. 2008;4(2):91–101.
58. Khositseth S, Sudjaritjan N, Tananchai P, Ong-ajyuth S, Sitprija V, Thongboonkerd V. Renal magnesium wasting and tubular dysfunction in leptospirosis. Nephrol Dial Transplant. 2008;23(3):952–8.
59. Jha V, Chugh KS. Community-acquired acute kidney injury in Asia. Semin Nephrol. 2008;28(4):330–47.
60. Kanjanabuch T, Sitprija V. Snakebite nephrotoxicity in Asia. Semin Nephrol. 2008;28(4):363–72.
61. Pinho FM, Zanetta DM, Burdmann EA. Acute renal failure after Crotalus durissus snakebite: a prospective survey on 100 patients. Kidney Int. 2005;67(2):659–67.
62. Silva GBDJ, Vasconcelos AGJ, Rocha AMT, Vasconcelos VR, Barros JN, Fujishima JS, et al. Acute kidney injury complicating bee stings – a review. Rev Inst Med Trop Sao Paulo. 2017;59:e25.
63. Xie C, Xu S, Ding F, Xie M, Lv J, Yao J, et al. Clinical features of severe wasp sting patients with dominantly toxic reaction: analysis of 1091 cases. PLoS One. 2013;8(12):e83164.
64. Sovann K. Acute kidney injury due to fish gallbladder ingestion: a case report from Cambodia. Blood Purif. 2017;44(Suppl 1):22–5.
65. Reimann HA, Sukaton RU. Djenkol bean poisoning (djenkolism); a cause of hematuria and anuria. Am J Med Sci. 1956;232(2):172–4.
66. Bye SN, Coetzer TH, Dutton MF. An enzyme immunoassay for atractyloside, the nephrotoxin of Callilepis laureola (Impila). Toxicon. 1990;28(8):997–1000.
67. Seedat YK, Hitchcock PJ. Acute renal failure from Callilepsis laureola. S Afr Med J. 1971;45(30):832–3.
68. Lee KG. Star fruit intoxication with acute kidney injury. Clin Med (Lond). 2012;12(5):494.
69. McClain JL, Hause DW, Clark MA. Amanita phalloides mushroom poisoning: a cluster of four fatalities. J Forensic Sci. 1989;34(1):83–7.
70. Gao H, Yang ZS, Jin SX. Primary observations on distal renal tubule acidosis in 177 cases caused by gossypol intoxication. Zhonghua Nei Ke Za Zhi. 1985;24(7):419–21, 47.
71. Yang B, Xie Y, Guo M, Rosner MH, Yang H, Ronco C. Nephrotoxicity and Chinese herbal medicine. Clin J Am Soc Nephrol. 2018;13(10):1605–11.
72. Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. Br J Clin Pharmacol. 2011;72(5):745–57.
73. Wunnapuk K, Mohammed F, Gawarammana I, Liu X, Verbeeck RK, Buckley NA, et al. Prediction of paraquat exposure and toxicity in clinically ill poisoned patients: a model based approach. Br J Clin Pharmacol. 2014;78(4):855–66.
74. Isha IT, Alam Z, Shaha BK, Bari MS, Bari MZJ, Chowdhury FR. Paraquat induced acute kidney injury and lung fibrosis: a case report from Bangladesh. BMC Res Notes. 2018;11(1):344.
75. Okuonghae HO, Ighogboja IS, Lawson JO, Nwana EJ. Diethylene glycol poisoning in Nigerian children. Ann Trop Paediatr. 1992;12(3):235–8.
76. Singh J, Dutta AK, Khare S, Dubey NK, Harit AK, Jain NK, et al. Diethylene glycol poisoning in Gurgaon, India, 1998. Bull World Health Organ. 2001;79(2):88–95.
77. Dambal A, Lakshmi KS, Gorikhan G, Umadi MM, Kalsad ST, Madhavaranga MP, et al. Obstetric acute kidney injury; a three year experience at a medical college hospital in North Karnataka, India. J Clin Diagn Res. 2015;9(3):OC01–4.
78. Prakash J, Niwas SS, Parekh A, Pandey LK, Sharatchandra L, Arora P, et al. Acute kidney injury in late pregnancy in developing countries. Ren Fail. 2010;32(3):309–13.
79. Dahiya A, Pannu N, Soranno DE. Sex as a biological variable in acute kidney injury. Curr Opin Crit Care. 2023;29(6):529–33.
80. Abdel Hakeem GL, Abdel Naeem EA, Swelam SH, El Morsi Aboul Fotoh L, El Mazary AA, Abdel Fadil AM, et al. Detection of occult acute kidney injury in Glucose-6-phosphate dehydrogenase deficiency anemia. Mediterr J Hematol. Infect Dis. 2016;8(1):e2016038.
81. Vasuvattakul S, Yenchitsomanus PT, Vachuanichsanong P, Thuwajit P, Kaitwatcharachai C, Laosombat V, et al. Autosomal recessive distal renal tubular acidosis associated with southeast Asian ovalocytosis. Kidney Int. 1999;56(5):1674–82.
82. Chugh KS, Jain S, Sakhuja V, Malik N, Gupta A, Gupta A, et al. Renovascular hypertension due to Takayasu's arteritis among Indian patients. Q J Med. 1992;85(307–308):833–43.

83. Thenabadu PN, Rajasuriya K, Wickremasinghe HR. Non-specific arteritis of the aorta and its main branches. Br Heart J. 1970;32(2):181–8.
84. Teoh PC, Tan LK, Chia BL, Chao TC, Tambyah JA, Feng PH. Non-specific aorto-arteritis in Singapore with special reference to hypertension. Am Heart J. 1978;95(6):683–90.
85. Cerda J, Bagga A, Kher V, Chakravarthi RM. The contrasting characteristics of acute kidney injury in developed and developing countries. Nat Clin Pract Nephrol. 2008;4(3):138–53.
86. Mi E, Mi E, Jeggo M. Where to now for one health and Ecohealth? EcoHealth. 2016;13(1):12–7.
87. Regmi K, Kunwar A, Ortega L. A systematic review of knowledge, attitudes and beliefs about malaria among the South Asian population. Infect Ecol Epidemiol. 2016;6:30822.
88. Chawla LS, Abell L, Mazhari R, Egan M, Kadambi N, Burke HB, et al. Identifying critically ill patients at high risk for developing acute renal failure: a pilot study. Kidney Int. 2005;68(5):2274–80.
89. Goldstein SL, Chawla LS. Renal angina. Clin J Am Soc Nephrol. 2010;5(5):943–9.
90. Kulvichit W, Sarnvanichpitak K, Peerapornratana S, Tungsanga S, Lumlertgul N, Praditpornsilpa K, et al. In-hospital mortality of critically ill patients with interactions of acute kidney injury and acute respiratory failure in the resource-limited settings: Results from SEA-AKI study. J Crit Care. 2022;71:154103.
91. Sukmark T, Lumlertgul N, Peerapornratana S, Khositrangsikun K, Tungsanga K, Sitprija V, et al. THAI-LEPTO-on-admission probability (THAI-LEPTO) score as an early tool for initial diagnosis of leptospirosis: result from Thai-Lepto AKI study group. PLoS Negl Trop Dis. 2018;12(3):e0006319.
92. Temeiam N, Jareinpituk S, Phinyo P, Patumanond J, Srisawat N. Development and validation of a simple score for diagnosis of leptospirosis at outpatient departments. PLoS Negl Trop Dis. 2020;14(1):e0007977.
93. Saravu K, Rishikesh K, Parikh CR. Risk factors and outcomes stratified by severity of acute kidney injury in malaria. PLoS One. 2014;9(3):e90419.
94. Mallhi TH, Sarriff A, Adnan AS, Khan YH, Hamzah AA, Jummaat F, et al. Dengue-induced Acute Kidney Injury (DAKI): A Neglected and Fatal Complication of Dengue Viral Infection--A Systematic Review. J Coll Physicians Surg Pak. 2015;25(11):828–34.
95. Aye KP, Thanachartwet V, Soe C, Desakorn V, Thwin KT, Chamnanchanunt S, et al. Clinical and laboratory parameters associated with acute kidney injury in patients with snakebite envenomation: a prospective observational study from Myanmar. BMC Nephrol. 2017;18(1):92.
96. Basu RK, Zappitelli M, Brunner L, Wang Y, Wong HR, Chawla LS, et al. Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. Kidney Int. 2014;85(3):659–67.
97. Srisawat N, Praditpornsilpa K, Patarakul K, Techapornrung M, Daraswang T, Sukmark T, et al. Neutrophil gelatinase associated Lipocalin (NGAL) in leptospirosis acute kidney injury: a multicenter study in Thailand. PLoS One. 2015;10(12):e0143367.
98. Nisansala T, Weerasekera M, Ranasinghe N, Marasinghe C, Gamage C, Fernando N, et al. Importance of KIM-1 and MCP-1 in determining the leptospirosis-associated AKI: a Sri Lankan study. Biomed Res Int. 2021;2021:1752904.
99. Liborio AB, Braz MB, Seguro AC, Meneses GC, Neves FM, Pedrosa DC, et al. Endothelial glycocalyx damage is associated with leptospirosis acute kidney injury. Am J Trop Med Hyg. 2015;92(3):611–6.
100. Limothai U, Dinhuzen J, Payongsri T, Tachaboon S, Tangkijvanich P, Chuaypen N, et al. Circulating microtranscriptome profiles reveal distinct expression of microRNAs in severe leptospirosis. PLoS Negl Trop Dis. 2020;14(11):e0008809.
101. Dinhuzen J, Limothai U, Tachaboon S, Krairojananan P, Laosatiankit B, Boonprasong S, et al. A prospective study to evaluate the accuracy of rapid diagnostic tests for diagnosis of human leptospirosis: result from THAI-LEPTO AKI study. PLoS Negl Trop Dis. 2021;15(2):e0009159.
102. Jirawannaporn S, Limothai U, Tachaboon S, Dinhuzen J, Kiatamornrak P, Chaisuriyong W, et al. Rapid and sensitive point-of-care detection of Leptospira by RPA-CRISPR/Cas12a targeting lipL32. PLoS Negl Trop Dis. 2022;16(1):e0010112.
103. Ratnayake I, Mohamed F, Buckley NA, Gawarammana IB, Dissanayake DM, Chathuranga U, et al. Early identification of acute kidney injury in Russell's viper (Daboia russelii) envenoming using renal biomarkers. PLoS Negl Trop Dis. 2019;13(7):e0007486.
104. Dantas RT, Sampaio TL, Lima DB, Menezes R, Canuto JA, Toyama MH, et al. Evaluation of KIM-1 as an early biomarker of snakebite-induced AKI in mice. Toxicon. 2018;151:24–8.
105. Chandrasekar T, Sharma A, Tennent L, Wong C, Chamberlain P, Abraham KA. A whole system approach to improving mortality associated with acute kidney injury. QJM. 2017;110(10):657–66.
106. Wilson FP, Shashaty M, Testani J, Aqeel I, Borovskiy Y, Ellenberg SS, et al. Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Lancet. 2015;385(9981):1966–74.
107. Colpaert K, Hoste EA, Steurbaut K, Benoit D, Van Hoecke S, De Turck F, et al. Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. Crit Care Med. 2012;40(4):1164–70.
108. Lachance P, Villeneuve PM, Rewa OG, Wilson FP, Selby NM, Featherstone RM, et al. Association between e-alert implementation for detection of acute kidney injury and outcomes: a systematic review. Nephrol Dial Transplant. 2017;32(2):265–72.

2 Climate Change and the Risk of Illness

Clara Beatriz Costa da Silva,
Tibelle Freitas Mauricio, Tainara Chagas de Sousa,
Vanessa Emille Carvalho de Sousa Freire,
Tahissa Frota Cavalcante, Alexandre Cunha Costa,
and Rafaella Pessoa Moreira

2.1 Introduction

In the contemporary scientific landscape, climate change has emerged as a key factor in global public health dynamics. With changing climate patterns (marked mainly by high temperatures and changes in precipitation patterns) and the increasing number of extreme weather events (heavy rainfall, floods, earthquakes, hurricanes, droughts, and heat waves), the risk of illness or worsening of pre-existing conditions is expected [1].

This chapter presents the correlations between climate change and the increasing risk of illness. The analysis addresses the underlying physiological mechanisms, the observed epidemiological impacts, and the suggestions that support mitigation and adaptation to this emerging reality. We seek to highlight the complex interactions that shape the human health landscape in a world in constant climate change, such as the relationship between tropical diseases and such changes in our planet's climate. In order to better understand how climate and health are related, it is necessary to address some concepts of climatology and health, including the concepts of environment, climate, climate change, extreme weather events, disasters, and climate-sensitive diseases.

2.2 Climate and Health: Initial Concepts

The term "environment" refers to the "system of objects that we immediately perceive around us," which is a very broad concept [2]. In this chapter, we will adopt the following definition: "the environment is defined as the complex of relationships between the natural world and living beings, which influence the life and behavior of such beings." [3]

In the strict sense, "climate" is defined as the average weather or, more rigorously, as the statistical description in terms of the average and variability of relevant variables over a period, which can vary from months to thousands or millions of years. According to the World Meteorological Organization, the classic period for calculating the average of these variables is 30 years. For this

C. B. C. da Silva · T. C. de Sousa
V. E. C. de Sousa Freire · T. F. Cavalcante
R. P. Moreira (✉)
Instituto de Ciências da Saúde, Universidade da Integração Internacional da Lusofonia Afro-Brasileira (Unilab), Redenção, Ceará, Brazil
e-mail: rafaellapessoa@unilab.edu.br

T. F. Mauricio
Programa de Pós-Graduação em Enfermagem, Universidade Federal do Ceará (UFC), Fortaleza, Ceará, Brazil

A. C. Costa
Instituto de Engenharias e Desenvolvimento Sustentável, Universidade da Integração Internacional da Lusofonia Afro-Brasileira (Unilab), Redenção, Ceará, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_2

purpose, the variables often considered most relevant are temperature, precipitation, and wind [4]. Regarding the concept of "climate change," it is understood as a change in the state of the climate that can be identified (e.g., through statistical tests) through variations in the average and/or variability of its properties and that persists for a prolonged period, generally decades or even longer. Climate change can be related to internal natural processes or external forces, such as modulations of solar cycles, volcanic eruptions, and persistent changes in the composition of the atmosphere or in land use caused by human action [4]. It is important to note that the main causes of global climate change are due to anthropogenic actions through net emissions of greenhouse gases (GHG) and aerosols, resulting from energy use, land use, and changes in land use, human lifestyles, and consumption and production patterns between regions, countries, and individuals [5, 6]. It is also essential to understand the term "extreme weather events," which refers to the occurrence of a meteorological or climate variable above (or below) a limit close to the upper (or lower) ends of the variable's change range [4].

Equally relevant is the concept of "disasters," which constitute serious changes in the normal functioning of a community or society as a result of dangerous physical events associated with vulnerable social conditions, causing a widespread dissemination of adverse human, material, economic, or environmental effects that require an immediate emergency response to meet critical human needs and that may require external support for recovery [4]. Added to these concepts is the concept of "climate-sensitive diseases," which refers to some health conditions that are influenced by the climate or geographic region [7].

2.3 Influence of Climate Change on Human Health

Studies show that climate change has a direct and indirect impact on human health. Globally, there are several studies conducted by researchers from different areas (exact, legal, social, and biological sciences) in order to increase interdisciplinary research, which aims to better understand the interrelationships between living beings and the environment in which we live [8].

Regarding human health, the effects of climate change can be divided into three mechanisms: direct, indirect, and social [9]. Physiological stress due to heat waves may be a possible direct effect, while the indirect effect can be exemplified by changes in air quality due to climate issues, while the social effect can be represented by migrations resulting from conflicts of climate origin [5].

Susceptibility to climate-related diseases has become a very important issue of global interest, given that climate change is one of the greatest threats to human health and economic development [9], since extreme weather events contribute to the emergence of health problems and to the increased incidence and spread of diseases, such as vector-borne tropical diseases. The literature has shown that the impacts of climate on human health are inevitable [10].

One piece of evidence of climate change can be seen in the increase in the average temperature of the Earth. Between 2011 and 2020, the temperature rose by approximately 1.1 °C compared to the period 1850 to 1900, when the increase was greater over land than over the oceans, causing phenomena such as desertification, changes in the hydrological cycle, and an increase in the frequency and intensity of extreme weather events [6, 8], which has several implications for health. From this perspective, studies reveal that most of the effects of climate change on health are related to complex mechanisms that harm all organs and systems of the human body. For example, exposure to extreme heat is one of the main risk factors for health, associated with dehydration, tissue damage, changes in membranes and cellular processes, as well as protein denaturation [11]. Although the human body has the ability to adapt to heat in order to ensure the survival of the individual, its capacity for adaptation is limited. It is suggested that the limits of human survival to heat could vary between

~25.8 °C and 34.1 °C in young people and ~21.9 °C and 33.7 °C in the elderly [12]. In addition, climate change may also worsen an existing condition and increase the vulnerability of individuals and communities [4].

In this context, the health sector is increasingly aware of the intrinsic relationship between climate change and human health. Thus, in 2019, the World Health Organization (WHO) defined air pollution and climate change as health priorities [13].

Furthermore, over the years, significant progress has been made in the integration between the health sector and the nationally determined contributions (NDCs) and long-term low emissions development strategies (LEDS), which are the main policy instruments for reducing emissions and increasing climate resilience, as recommended by the Paris Agreement [10]. In 2022, 91% of the available NDCs included health considerations, compared to 70% of the 2019 reports. In contrast to previous rounds of national climate plans, considerably more inclusive and health-promoting climate targets and policies have been developed for mitigation, adaptation, means of implementation, loss and damage, and long-term sustainable development strategies [14]. In relation to the morbidity and mortality profile associated with climate change, climate-sensitive diseases (CSDs) constitute a public health problem for several countries, mainly for developing countries and for poor countries in drylands. These sets of diseases are directly or indirectly, temporarily, or geographically driven by climate [15]. In this context, it is essential to understand which climate variables can contribute to the incidence of diseases and how this process occurs. However, the purpose of this chapter is not necessarily to exhaust all the variables and processes involved in the relationship between climate and health, given the complexity and diversity of the interactions involved. Instead, the aim is to provide an initial and enlightening view of this relationship, recognizing the challenges inherent in understanding it, highlighting the main points of connection, and providing a basis for future research.

It is important to note that climate events disproportionately harm the most vulnerable groups (children, the elderly, ethnic minorities, low-income communities, and people with underlying health problems) [16, 17]. In view of this, three hypotheses have been presented in the literature regarding the adverse effects of temperature and pollution on specific subgroups. The first refers to differential exposure, suggesting that disadvantaged socioeconomic groups are more exposed. The second hypothesis involves differential susceptibility, indicating that people with precarious conditions may be more susceptible to the adverse effects of climate change, mainly due to the difficulty of accessing healthcare. The third hypothesis proposes a multiplicative combination of these factors, where greater exposure and susceptibility amplify each other [18].

It is worth noting that, in addition to its relationship with climate change, socioeconomic vulnerability is an important social determinant of health related to several diseases, such as diabetes mellitus [19], cardiovascular diseases [20], and obesity [21], and is also associated with neglected tropical diseases, since poverty and poor sanitation conditions can influence the transmission of parasites [22].

A summary of the effects of climate change, vectors/agents of tropical diseases, and risk factors for chronic diseases was carried out, according to exposure or susceptibility in the most vulnerable groups, represented in Fig. 2.1.

Next, we will explore how climate can influence specific diseases, with a special focus on chronic diseases, kidney diseases, and tropical diseases, providing a more comprehensive understanding of the impacts of climate on human health.

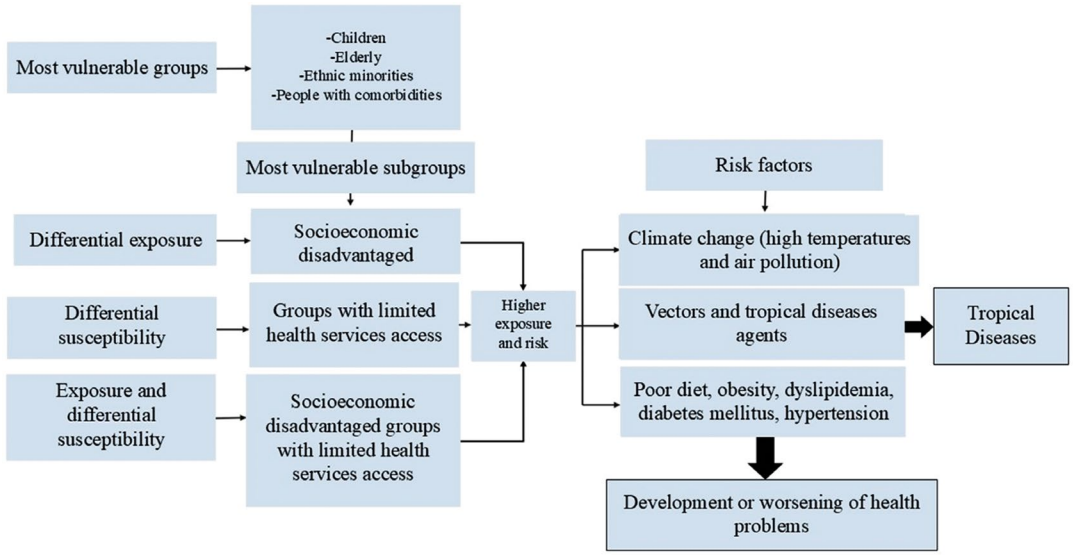


Fig. 2.1 Most vulnerable groups to the effects of climate change, vectors/agents of tropical diseases, and risk factors for chronic diseases, according to exposure or susceptibility

2.4 Influence of Climate on Chronic Diseases

Climate change has a profound impact on human health, directly and indirectly affecting many aspects of human well-being. This topic explores the mechanisms by which climate change influences health, presenting a comprehensive overview of current scientific evidence and discussing the policy and social responses needed to mitigate these impacts.

Climate variables, such as temperature, precipitation, and humidity, have been identified as important risk factors for cardiovascular disease (CVD). Exposure to extreme heat and cold can trigger adverse cardiovascular events, while air pollution, especially in industrialized areas, is associated with the progression of these diseases [23].

Studies demonstrate associations between climate variations and biological rhythms in plasma lipids and lipoproteins, as well as in hospitalization rates for CVD. Seasonality influences cholesterol and triglyceride levels, as well as the occurrence of cardiovascular hospitalizations [24–26].

Physiological effects of extreme temperatures on CVD vary and include vasodilation and sweating in response to heat, while exposure to cold leads to vasoconstriction and increased stimulation of the sympathetic nervous system. These responses can trigger cardiovascular events, such as acute myocardial infarction and arterial hypertension [27–29].

Climate change can also affect metabolic function in people with diabetes mellitus (DM). In colder temperatures, insulin sensitivity increases, while in warmer temperatures and with greater relative humidity, dehydration can occur, leading to increases in blood glucose concentrations [30].

Consequently, climate change can increase the vulnerability of people with DM to extreme weather events and impair their ability to respond to heat stress. Recent studies have shown associations between temperature changes and hospitalizations due to complications in patients with DM [31–33]. Furthermore, natural disasters related to climate change can also contribute to an increase in complications associated with DM, as it was evidenced after Hurricane Katrina in 2015. Disasters reduce access to health services

and essential medicines, in addition to triggering psychological stress in survivors, impacting the management of individuals with diabetes who are particularly vulnerable to infections and hospitalizations [34]. Finally, it is worth highlighting the presence of common conditions between climate change and DM, such as rapid urbanization and the increase in the production of ultra-processed foods, which contribute to an increased risk of DM [35, 36]. Exposure to climate variables is also associated with the worsening of respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD). It is widely reported that air pollution has deleterious effects on the respiratory health of individuals [37–41]. However, studies with more in-depth analyses in several regions of the world, including Latin America and China, reveal less obvious nuances. For clarification, each increase in the concentration of air pollutants, such as particulate matter (PM2.5), is associated with an increased risk of mortality or hospitalization due to respiratory diseases [37–41]. In addition, pollutants such as nitrogen dioxide (NO_2) and carbon monoxide (CO) are identified as risk factors for lung infections, COPD, and asthma, especially in women [40, 41].

Climate change also contributes directly and indirectly to the development or worsening of cancer. Studies have shown associations between annual exposure to air pollutants and an increased risk of lung cancer and other types of cancer [42–45]. In addition, intensifications of risk factors, such as exposure to ultraviolet radiation, natural disasters, and abnormal temperatures, are increasingly being considered as possible influences on the development of cancer [46, 47].

It is worth noting that cancer patients face additional challenges related to regulating body temperature and immune function, making them more vulnerable to the effects of extreme weather conditions [48, 49]. Additionally, the occurrence of disasters, a factor previously discussed in the topic on DM, can also affect the provision of care and access to treatments for cancer patients [50, 51].

In this topic, it was possible to observe the influence of climate on several chronic diseases. In the next topic, we will give special emphasis to kidney diseases.

2.5 Influence of Climate on Kidney Diseases

Climate change can significantly impact kidney health. Studies have shown that the incidence of acute kidney injury (AKI), chronic kidney disease (CKD), and kidney stones can increase due to exposure to heat stroke and heat stress [52]. Research also highlights an increase in hospital admissions for these causes during periods of high temperatures [53, 54].

A study conducted in the USA observed significant complications in patients hospitalized for heat stroke who developed AKI, such as the need for invasive mechanical ventilation and blood transfusion [55]. In these patients, an association was also found between heat stress and various types of organ failure, sepsis, electrolyte and acid-base disorders, acute myocardial infarction, cardiac arrest, and in-hospital death. Mechanisms such as renal hypoperfusion, severe dehydration, myoedema, and myocardial dysfunction are related to AKI due to heat stroke. Furthermore, increased body temperature can induce inflammation, dehydration, and an increased risk of kidney stone formation due to higher urine concentration, contributing to the development of CKD [56–59]. In addition to high temperatures, studies also indicate a relationship between exposure to low temperatures and increased renal mortality, as evidenced by a study conducted in Japan [60].

Air pollution has also been associated with negative impacts on kidney health. Prolonged exposure to pollutants such as particulate matter (PM10, PM2.5), NO_2, and other elements such as PM1, CO, SO_2, and O_3 has been related to an increased risk of kidney disease [59, 61–64]. Thus, exposure to pollutants aggravates kidney disease due to increased blood pressure, oxida-

tive stress, inflammatory response, and metabolic changes. This is especially relevant considering the negative impact of climate change on cardiovascular disease and diabetes mellitus, the main risk factors for kidney disease [61, 65].

2.6 Influence of Climate on Tropical Diseases

Climate change is estimated to influence all scales of biological, social, ecological, and geographic organization, interfering globally in the phenology of various organisms and affecting the complex and interactive network of ecosystems, which results in impacts on the ecology of hosts, parasites, and vectors, both in time and space [66].

Studies indicate that climate change may create asynchrony either by changing the behavior of hosts or by making it difficult for them to be available at the time needed to complete the life cycle. Consequently, this asynchrony may reduce the disease in the short term or may put selective pressure on parasites, selecting variants that drive the host to expel transmission phases at a time appropriate to the new system [66].

In a systematic review on the impact of climate change on neglected tropical diseases (NTDs), it was identified that most studies discussed the effect of climate change on dengue virus and the Chikungunya infection. The most frequently discussed factors associated with climate change were temperature and precipitation [67].

Temperature was associated with an increase in the vector's development rate and the frequency of mosquito bites. However, as the temperature exceeded the vector's thermotolerant range, the transmitter's growth and survival decreased. In this same study, it was observed that humidity and rising sea levels were also factors that could impact the distribution of vectors and disease transmission [67]. Thus, tropical areas contribute to the proliferation of mosquitoes that transmit the arboviruses dengue, Zika, and chikungunya [68, 69].

Furthermore, in semiarid regions, periods of drought without adequate access to drinking water increase the risk of other waterborne diseases such as giardiasis, hepatitis A, and diarrheal diseases [70, 71]. Given this problem, control and prevention measures must be urgently implemented by health professionals and authorities responsible for public health at the national level.

Climate change significantly influences the dynamics of tropical diseases, since the characteristics of the life history of many species of organisms involved in the life cycles of these diseases are associated with the environmental scenario. Therefore, it is necessary to understand the effects of climate on tropical diseases [66].

2.7 Perspectives for a Healthier Future

It is clear that climate change significantly impacts human health, which is evident with climate-sensitive diseases, material damage, and compromised health services. Therefore, it is essential to urgently implement public policies to mitigate these impacts.

Health interventions that take into account the different levels of management responsible, which include the macro, meso, and micro levels, are extremely important to address the effects of climate change on human health. The macro level is represented by the participation of national and international health systems, such as the development of epidemiological models and policies sensitive to climate change. The meso level is characterized by government collaboration in the development of risk maps, investment in renewable energy, and urban greening. Finally, the micro level is mentioned, which involves the participation of the individual, the community, and the professionals, characterized by the provision of health education and specific examinations for emerging health problems [72]. Furthermore, policies focused on healthy diets, sustainable agriculture, and urban planning that promotes safe physical activity can reduce the risks of

climate-related diseases [72, 73]. It is also crucial to include vulnerability assessment and adaptation to climate change, especially for the most vulnerable groups, as well as the design and implementation of appropriate health interventions [74]. These and other measures are essential to address the imminent challenges posed by climate change and protect public health in the long term.

2.8 Take-Home Message

- It is essential to elaborate plans for different levels of public management that include the implementation of effective interventions to address the effects of climate change on human health.
- Implementation of public policies, such as access to clean water and basic sanitation, to reduce the impacts of climate change on health, especially in the most vulnerable groups.
- Strengthening health promotion, within the scope of primary care, focused on the influence of climate change on human health.
- Planning and implementation of health services with health teams trained to act in the prevention of the development or worsening of chronic diseases, such as kidney diseases, and tropical diseases, resulting from climate change.

2.9 Financial Support

This study received funding from Conselho Nacional de Desenvolvimento Científico e Tecnológico—Brazil (CNPq, call CNPq/MCTI process no. 402514/2021–1; CNPq, Brazil, call CNPq/MCTI process no. 403732/2023–9); Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico (FUNCAP) e CAPES/Brazil/Ministry of Education (CAPES/FUNCAP, Brazil, no. 18/2020 Programa de Desenvolvimento da Pós-Graduação "Parcerias Estratégicas nos Estados"); and FUNCAP (call FUNCAP INTERNACIONALIZAÇÃO 08/2023).

References

1. Intergovernmental Panel On Climate Change (IPCC). Climate change 2021: the physical science basis – contribution of working group I to the sixth assessment report of the intergovernmental panel on climate change. Cambridge: Cambridge University Press; 2021.
2. Holzer W. Uma discussão fenomenológica sobre os conceitos de paisagem e lugar, território e meio ambiente. Revista Território. 1997;2(3):77–85.
3. Giudice M. Disciplina constitucional do meio ambiente e rápida visão das formas de apenação pela degradação ambiental. Revista do Tribunal Regional Federal da 1ª Região. Brasília. 1994;6(2):33–50.
4. IPCC, 2018: Annex I: Glossary [Matthews, J.B.R. (ed.)]. In: Global Warming of 1.5°C. An IPCC Special Report on the impacts of global warming of 1.5°C above pre-industrial levels and related global greenhouse gas emission pathways, in the context of strengthening the global response to the threat of climate change, sustainable development, and efforts to eradicate poverty [Masson-Delmotte, V., P. Zhai, H.-O. Pörtner, D. Roberts, et al.]. Cambridge University Press, Cambridge/New York, pp. 541–562. Available from: https://doi.org/10.1017/9781009157940.008.
5. Vassari-Pereira D, Valverde MC, Asmus GF. Impact of climate change and air quality on hospitalizations for respiratory diseases in municipalities in the metropolitan region of São Paulo (MRSP). Brazil Ciência e Saúde Coletiva. 2022. Available from:;27(05):2023. https://doi.org/10.1590/1413-81232022275.08632021.
6. IPCC. Sections. In: Core Writing Team, Lee H, Romero J, editors. Climate change 2023: synthesis report. Contribution of working groups I, II and III to the sixth assessment report of the intergovernmental panel on climate change. Geneva: IPCC; 2023. p. 35–115. https://doi.org/10.59327/IPCC/AR6-9789291691647.
7. de Sousa TCM, Amancio F, Hacon SS, Barcellos C. Doenças sensíveis ao clima no Brasil e no mundo: revisão sistemática [Climate-sensitive diseases in Brazil and the world: systematic review. Enfermedades sensibles al clima en Brasil y el mundo: revisión sistemática]. Rev Panam Salud Publica. 2018;42:e85. Portuguese. https://doi.org/10.26633/RPSP.2018.85.
8. Barcellos C, Hacon S d S. Um grau e meio. E daí? Cad Saude Publica. 2016;32(3):e00212315. Available from: https://doi.org/10.1590/0102-311X00212315.
9. Smith KR, Woodward A, Campbell-Lendrum D, Chadee DD, Honda Y, Liu Q, Olwoch JM, Revich B, Sauerborn R. Human health: impacts, adaptation, and co-benefits. In: Climate change 2014: impacts, adaptation, and vulnerability. Part A: global and sectoral aspects. Contribution of working group II to the fifth assessment report of the intergovernmental panel on climate change, vol. 2014. Cambridge/New York: Cambridge University Press; 2014. p. 709–54.

10. Organização Pan-Americana da Saúde. A saúde precisa estar no centro dos planos nacionais de combate às mudanças climáticas. 2023. Available from: https://www.paho.org/pt/noticias/23-11-2023-saude-precisa-estar-no-centro-dos-planos-nacionais-combate-mudancas-climaticas.
11. Ahima RS. Global warming threatens human thermoregulation and survival. J Clin Invest. 2020;130(2):559–61.
12. Vanos J, Guzman-Echavarria G, Baldwin JW, Bongers C, Ebi KL, Jay O. A physiological approach for assessing human survivability and liveability to heat in a changing climate. Nat Commun. 2023;14(1):7653.
13. Nações Unidas Brasil. OMS define 10 prioridades de saúde para 2019. Available from: https://brasil.un.org/pt-br/82146-oms-define-10-prioridades-de-sa%C3%BAde-para-2019.
14. Who health and climate change global survey report. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications/i/item/9789240038509.
15. Duarte JL. Influência da variabilidade climática e das alterações ambientais na ocorrência de doenças sensíveis ao clima em uma capital da Amazônia Ocidental brasileira. Universidade de São Paulo; 2017.
16. Intergovernmental Panel on Climate Change. Summary for policymakers. In: Global warming of 1.5°C. 2018. Available from: https://www.ipcc.ch/sr15/.opensinnewtab.
17. Watts N, Amann M, Arnell N, et al. The 2020 report of the Lancet countdown on health and climate change: responding to converging crises. Lancet. 2021;397:129–70.
18. Rodrigues PCO, Ignotti E, Hacon SS. Socioeconomic factors increase the adverse effects of air pollution and temperature on mortality. Rev Bras Epidemiol. 2019;22:e190011. Portuguese, English. https://doi.org/10.1590/1980-549720190011.
19. Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, Thornton PL, Haire-Joshu D. Social determinants of health and diabetes: a scientific review. Diabetes Care. 2020;44(1):258–79.
20. Kreatsoulas C, Anand SS. The impact of social determinants on cardiovascular disease. Can J Cardiol. 2010;26(Suppl C):8C–13C.
21. Anekwe CV, Jarrell AR, Townsend MJ, Gaudier GI, Hiserodt JM, Stanford FC. Socioeconomics of obesity. Curr Obes Rep. 2020;9(3):272–9.
22. Magalhães AR, Codeço CT, Svenning JC, Escobar LE, Van de Vuurst P, Gonçalves-Souza T. Neglected tropical diseases risk correlates with poverty and early ecosystem destruction. Infect Dis Poverty. 2023;12(1):32.
23. Liu J, Varghese BM, Hansen A, Zhang Y, et al. Heat exposure and cardiovascular health outcomes: a systematic review and meta-analysis. Lancet Planet Health. 2022;6(6):e484–95.
24. Aryal A, Harmon AC, Dugas TR. Particulate matter air pollutants and cardiovascular disease: strategies for intervention. Pharmacol Ther Oxford. 2021;223:107890.
25. Corozolla W, Vhs Z, Fal M, et al. Associations of plasma lipids, lipoproteins, and cardiovascular outcomes with climatic variations in a large Brazilian population of Campinas, São Paulo state: an eight-year study. Braz J Med Biol Res. 2021;54(10):e11035. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8365875/.
26. Silveira IH. Efeitos da temperatura na mortalidade por doenças cardiovasculares e impactos futuros segundo cenários de mudanças climáticas no Brasil. Tese Doutorado. 2018:144f.
27. Peña R, Valdés M, Nazzal C. Efecto de las temperaturas extremas en la incidencia de enfermedades cardiovasculares: revisión bibliográfica 2016–2022. Rev Chil Cardiol [Internet]. 2022 Abr [citado 2024 Ene 08]; 41(1): 51–64. Disponible en: http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0718-85602022000100051&lng=es. https://doi.org/10.4067/S0718-85602022000100051.
28. Johansson S, Rosengren A, Young K, et al. Mortality and morbidity trends after the first year in survivors of acute myocardial infarction: a systematic review. BMC Cardiovasc Disord. 2017;17(1):53.
29. Mohammadi R, Soori H, Alipour A, et al. The impact of ambient temperature on acute myocardial infarction admissions in Tehran, Iran. J Therm Biol. 2018;73:24–31.
30. Wainstock T, Israel Y. Pregnant women may be sweeter in the summer: seasonal changes in glucose challenge tests results. A population-based study. Diabetes Res Clin Pract Amsterdam. 2019;147:134–7.
31. Ratter-Rieck JM, Roden M, Herder C. Diabetes and climate change: current evidence and implications for people with diabetes, clinicians and policy stakeholders. Diabetologia, Berlim. 2023;66(6):1003–15.
32. Lam HCY, Chan JCN, Luk AOY, Chan EYY, Goggins WB. Short-term association between ambient temperature and acute myocardial infarction hospitalizations for diabetes mellitus patients: a time series study. PLoS Med. 2018;15(7):e1002612. Published 2018 Jul 17.
33. Hajat S, Haines A, Sarran C, Sharma A, Bates C, Fleming LE. The effect of ambient temperature on type-2-diabetes: case-crossover analysis of 4+ million GP consultations across England. Environ Health. 2017;16(1):73.
34. BMC. Medicine. Diabetes and climate change: breaking the vicious cycle. BMC Med. 2023;21(1):281.
35. Al-Shihabi F, Moore A, Chowdhury TA. Diabetes and climate change. Diabet Med. 2023;40(3):e14971. https://doi.org/10.1111/dme.14971.
36. Dain K, Hadley L. Diabetes and climate change—two interconnected global challenges. Diabetes Res Clin Pract. 2012;97:337–9.
37. Pacheco SE, Guidos-Fogelbach G, Annesi-Maesano I, et al. Climate change and global issues in allergy and immunology. J Allergy Clin Immunol. 2021;148(6):1366–77. https://doi.org/10.1016/j.jaci.2021.10.011.
38. Renzi M, Scortichini M, Forastiere F, et al. A nationwide study of air pollution from particulate matter and

daily hospitalizations for respiratory diseases in Italy. Sci Total Environ. 2022;807:151034.
39. Fajersztajn L, Saldiva P, Pereira LAA, et al. Short-term effects of fine particulate matter pollution on daily health events in Latin America: a systematic review and meta-analysis. Int J Public Health. 2017;62:729–38. https://doi.org/10.1007/s00038-017-0960-y.
40. Chang Q, Zhang H, Zhao Y. Ambient air pollution and daily hospital admissions for respiratory system–related diseases in a heavy polluted city in Northeast China. Environ Sci Pollut Res. 2020;27:10055–64.
41. Xie J, Teng J, Fan Y, et al. The short-term effects of air pollutants on hospitalizations for respiratory disease in Hefei, China. Int J Biometeorol. 2019;63:315–26.
42. Kamangar F, Nasrollahzadeh D, Safiri S, et al. The global, regional, and national burden of oesophageal cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet Gastroenterol Hepatol. 2020;5(6):582–97.
43. Yu P, Guo S, Xu R, et al. Cohort studies of long-term exposure to outdoor particulate matter and risks of cancer: a systematic review and meta-analysis. Innovation (Camb). 2021;2(3):100143.
44. Korsiak J, Pinault L, Christidis T, et al. Long-term exposure to wildfires and cancer incidence in Canada: a population-based observational cohort study. Lancet Planet Health. 2022;6(5):e400–9.
45. Hart JE, Bertrand KA, DuPre N. Long-term particulate matter exposures during adulthood and risk of breast cancer incidence in the nurses' health study II prospective cohort. Cancer Epidemiol Biomarkers Prev. 2016;25(8):1274–6.
46. Yu P, Xu R, Yang Z, et al. Cancer and ongoing climate change: who are the most affected? ACS Environ Au. 2022;3(1):5–11.
47. Bernhard GH, Neale RE, Barnes PW, et al. Environmental effects of stratospheric ozone depletion, UV radiation and interactions with climate change: UNEP environmental effects assessment panel, update 2019. Photochem Photobiol Sci. 2020;19(5):542–84.
48. Zhao Q, Guo Y, Ye T, et al. Global, regional, and national burden of mortality associated with non-optimal ambient temperatures from 2000 to 2019: a three-stage modelling study. Lancet Planet Health. 2021;5(7):e415–25.
49. Bikomeye JC, Beyer AM, Kwarteng JL, Beyer KMM. Greenspace, inflammation, cardiovascular health, and cancer: a review and conceptual framework for greenspace in cardio-oncology research. Int J Environ Res Public Health. 2022;19(4):2426.
50. Jessel S, Sawyer S, Hernández D. Energy, poverty, and health in climate change: a comprehensive review of an emerging literature. Front Public Health. 2019;7:357.
51. Rublee C, Bikomeye J, Rao S, et al. Climate mitigation and adaptation is cancer prevention and control. J Clim Change Health. 2023;10:100209.
52. Johnson RJ, Sánchez-Lozada LG, Newman LS, et al. Climate change and the kidney. Ann Nutr Metab. 2019;74(Suppl 3):38–44.
53. Borg M, Bi P, Nitschke M, et al. The impact of daily temperature on renal disease incidence: an ecological study. Environ Health. 2017;16(1):114.
54. Borg M, Nitschke M, Williams S, McDonald S, et al. Using the excess heat factor to indicate heatwave-related urinary disease: a case study in Adelaide, South Australia. Int J Biometeorol. 2019;63(4):435–47.
55. Thongprayoon C, Qureshi F, Petnak T, et al. Impact of acute kidney injury on outcomes of hospitalizations for heat stroke in the United States. Diseases. 2020;8(3):28.
56. Borghi L, Meschi T, Amato F, Novarini A, Romanelli A, Cigala F. Hot occupation and nephrolithiasis. J Urol. 1993;150(6):1757–60.
57. Sasai F, Roncal-Jimenez C, Rogers K, et al. Climate change and nephrology. Nephrol Dial Transplant. 2023;38(1):41–8.
58. Htay ZW, Ng CFS, Kim Y, et al. Associations between short-term exposure to ambient temperature and renal disease mortality in Japan during 1979–2019: a time-stratified case-crossover analysis. Environ Epidemiol. 2024;8(1):e293.
59. Helldén D, Andersson C, Nilsson M, et al. Climate change and child health: a scoping review and an expanded conceptual framework. Lancet Planet Health. 2021;5(3):e164–75.
60. Thongprayoon C, Petnak T, Kanduri SR, et al. Impact of rhabdomyolysis on outcomes of hospitalizations for heat stroke in the United States. Hosp Pract. 2020;48(5):276–81.
61. Li J, Dai L, Deng X, et al. Association between long-term exposure to low level air pollutants and incident end-stage kidney disease in the UK Biobank: a prospective cohort. Chemosphere. 2023;338:139470.
62. Wu G, Cai M, Wang C. Ambient air pollution and incidence, progression to multimorbidity and death of hypertension, diabetes, and chronic kidney disease: a national prospective cohort. Sci Total Environ. 2023;881:163406.
63. Liu L, Tian X, Zhao Y, et al. Long-term exposure to PM2. 5 and PM10 and chronic kidney disease: the Beijing health management cohort, from 2013 to 2018. Environ Sci Pollut Res. 2023;30(7):17817–27.
64. Li Q, Wang YY, Guo Y, et al. Association between airborne particulate matter and renal function: an analysis of 2.5 million young adults. Environ Int. 2021;147:106348.
65. Sapkota A, Kotanko P. Climate change-fuelled natural disasters and chronic kidney disease: a call for action. Nat Rev Nephrol. 2023;19:141–2.
66. Booth M. Climate change and the neglected tropical diseases. Adv Parasitol. 2018;100:39–126.
67. Tidman R, Abela-Ridder B, de Castañeda RR. The impact of climate change on neglected tropical diseases: a systematic review. Trans R Soc Trop Med Hyg. 2021;115(2):147–68.

68. Costa AC, Gomes TF, Moreira RP, Cavalcante TF, Mamede GL. Influence of hydroclimatic variability on dengue incidence in a tropical dryland area. Acta Trop. 2022;235:106657.
69. Soares PV, Araújo RAF, Almeida ME. A Influência das Variáveis Meteorológicas na Ocorrência de Casos de Dengue em Fortaleza. Ceará Rev Brasileira de Meteorologia. 2021;36:759–66.
70. Vitor GA, Lando GA, Duarte CAL, Marques DAV, D'Angelo IBM. Saúde e saneamento no Brasil: uma revisão narrativa sobre a associação das condições de saneamento básico com as doenças de veiculação hídrica. Res Soc Dev. 2021;10(15):e521101522913.
71. Merino VR, Nakano V, Delannoy S, Fach P, Alberca GGF, Farfan MJ, Piazza RMF, Avila-Campos MJ. Prevalence of enteropathogens and virulence traits in Brazilian children with and without diarrhea. Front Cell Infect Microbiol. 2020;10:1–8. https://doi.org/10.3389/fcimb.2020.549919.
72. Moreira RP, de Oliveira FBB, de Araujo TL, et al. Health interventions for preventing climate-sensitive diseases: scoping review. J Urban Health. 2022;99(3):519–32.
73. Zilbermint M. Diabetes and climate change. J Community Hosp Intern Med Perspect. 2020;10(5):409–12.
74. Romanello M, Di Napoli C, Drummond P, et al. The 2022 report of the Lancet countdown on health and climate change: health at the mercy of fossil fuels. Lancet. 2022;400(10363):1619–54.

3 Climate Change in the Tropics: Rising Temperatures and Kidney Health

Fabiana Baggio Nerbass, Jyana Gomes Morais, and Marcos Alexandre Vieira

3.1 Introduction

Climate change represents a significant threat to humanity. According to the World Health Organization, climate change is already a direct contributor to humanitarian emergencies resulting from heat waves, forest fires, floods, tropical storms, hurricanes, and other phenomena, and it is increasing in scale, frequency, and intensity. Populations living in tropical areas, especially those inhabiting regions with deficient health infrastructure, will continue to suffer the greatest consequences [1].

The kidneys play a fundamental role in protecting against climate-related morbidities due to their essential contribution to maintaining hydroelectrolytic balance. However, at the same time, they are among the organs most affected by high temperatures, which favor the occurrence of hydroelectrolytic imbalances, whether acute or chronic [2]. While acute dehydration leads to a decrease in the kidney's filtration ability and the possibility of acute kidney injury (AKI), chronic exposure to a state of water deficit is related to both the formation of kidney stones and cases of chronic kidney disease (CKD). Furthermore, at higher temperatures, the insects responsible for transmitting many tropical diseases, which are among the causes of AKI, produce more offspring, and parasites and viruses complete incubation more quickly [3].

Therefore, climate change should be a special concern for professionals working in nephrology, especially in the most vulnerable regions [2]. In a meta-analysis that included 82 epidemiological studies, for every 1 °C increase in temperature, there was a 1% increase in the risk of morbidity and 3% in mortality from renal causes. In addition, heat waves increased the risk of kidney disease proportionally to their intensity [4]. In Brazil, a publication with comprehensive national data showed that for every 1 °C increase in average temperature, the estimated risk of hospitalization for kidney disease increased by 0.9% [5].

In this chapter, we will address the effects of climate change, especially related to increased temperature and heat waves, in the current context and future projections related to AKI, CKD, and kidney stones.

3.2 Acute Kidney Injury

AKI is a clinical finding of multifactorial etiology, associated with high morbidity and mortality, with a significant economic impact on health care. It is the term described for the clinical condition that occurs when renal function is critically and acutely reduced to a point where the body accumulates uremic waste and becomes

F. B. Nerbass (✉) · J. G. Morais · M. A. Vieira
Fundação Pró-Rim, Joinville, Santa Catarina, Brazil
e-mail: fabiana.nerbass@prorim.org.br

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_3

unable to maintain adequate electrolyte, acid-base, and water balances [6]. It is estimated that 13.3 million episodes of AKI occur every year, with 85% of events occurring in low- and lower-middle-income regions [7].

AKI can be classified as prerenal, renal or intrinsic, and postrenal. According to the KDIGO (Kidney Disease: Improving Global Outcomes) definition, it is diagnosed by an absolute increase in serum creatinine of at least 0.3 mg/dL in 48 h or by a 50% increase in creatinine relative to the baseline value within 7 days or a urine volume of less than 0.5 mL/kg/h for at least 6 h [8]. In everyday life, the disease can be insidious, and the subclinical picture makes diagnosis difficult.

The relationship between AKI and increased ambient temperature has been shown to be consistent. A meta-analysis that included 25 epidemiological studies based on emergency room admissions and hospital admissions reported a 1.2% increase in AKI cases for every 1 °C rise in temperature [4]. In a study from England that included, in addition to secondary and tertiary care cases, AKI occurrences in the community through data provided by laboratories to the health system (e-alert), the estimated prevalence was almost double, 2% for every 1 °C increase in temperature. The same authors found a 62.3% higher probability of AKI on a day with a maximum temperature of 32 °C compared to a day with a maximum temperature of 17 °C [9]. Heat-related AKI has a higher incidence among the most vulnerable, such as the elderly, children, and economically disadvantaged communities [10, 11].

As shown in Fig. 3.1, climate change is expected to increase AKI cases in several ways, mainly due to the impacts on cases resulting from heat stress and dehydration and also secondary to infections, which have a significant influence on the occurrence of AKI worldwide. The impact of infectious diseases whose transmission is related to water, including dengue, leptospirosis, and

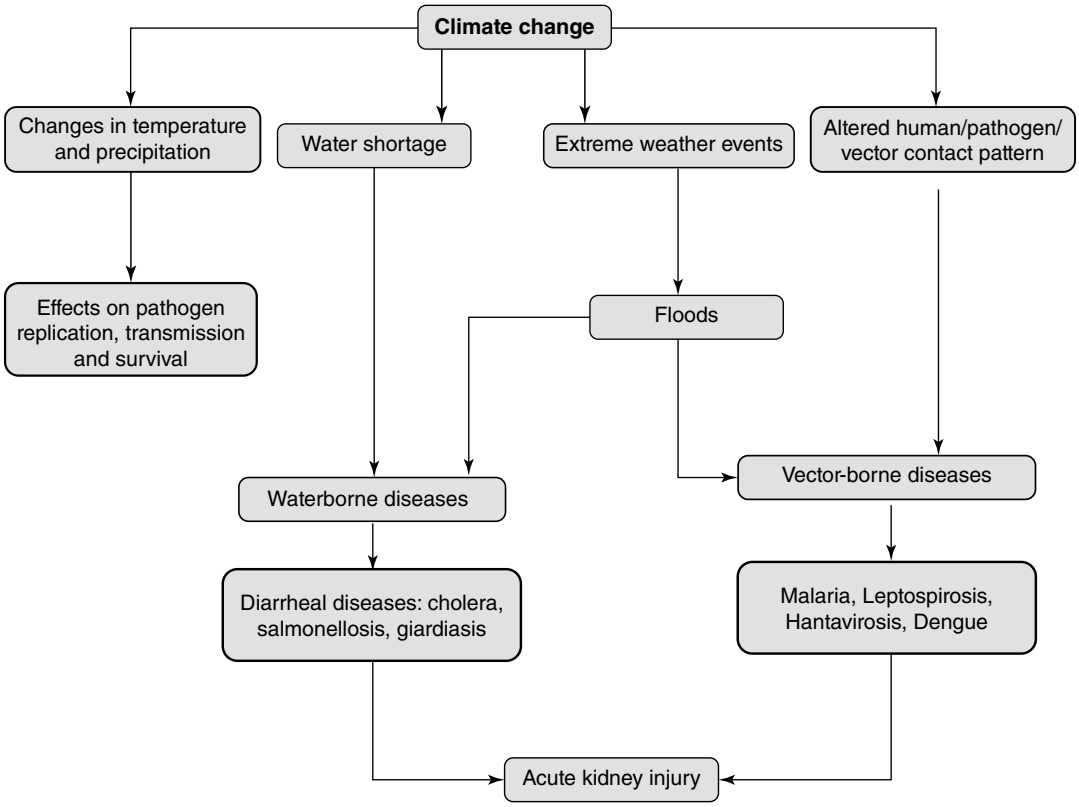


Fig. 3.1 Relationship between climate change, infectious diseases, and ARI. (Adapted from Young et al. [12])

diarrheal diseases, such as cholera, will probably increase due to the greater occurrence of floods and waterlogging [13]. In addition, in the presence of higher temperatures, vectors produce more offspring, and the incubation period of parasites and viruses is faster [3].

In regions with less infrastructure, the use of bedside tests can contribute to the care of the population and facilitate diagnosis, such as the assessment of urea nitrogen in saliva to track different stages of AKI [14].

3.2.1 AKI and Heat Stress

Heat stress occurs when physiological changes to maintain body temperature (such as sweat production) fail to prevent an increase in core body temperature. This condition is exacerbated when associated with intense physical exercise due to the generation of metabolic heat and is often accompanied by dehydration [2].

Heat stress, dehydration, and physical exercise decrease renal blood flow in humans, and even more profound reductions in perfusion are observed when these factors are combined [15]. These conditions can promote hyperthermia, localized ischemia, hypoxemia, and ATP depletion, increased demand for sodium reabsorption, increased intrarenal fructose production, and hyperuricemia. As shown in Fig. 3.2, collectively, these responses promote inflammation and oxidative stress, increasing the risk of AKI [15], a disease that, when increased in frequency, severity, and/or duration, increases the risk of developing or progressing to CKD [16].

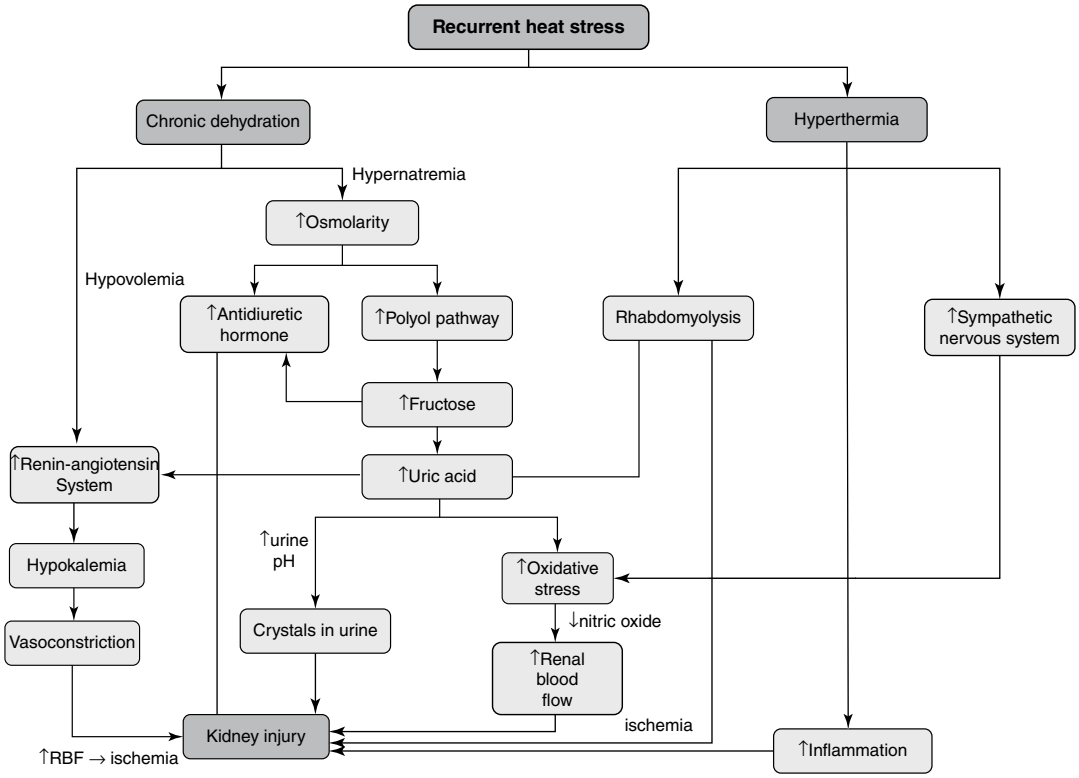


Fig. 3.2 Pathogenesis of CKD proposed by Sasai et al. [2] Heat stress can lead to CKD through two major pathways. One mechanism results from excessive sweating, leading to dehydration, extracellular volume depletion, and electrolyte abnormalities. The other major mechanism is the effects of hyperthermia, stimulating inflammation, energy depletion, and activation of the sympathetic nervous system and renin-angiotensin system. *RBF* renal blood flow

3.3 Chronic Kidney Disease

Chronic kidney disease (CKD) has a high prevalence worldwide. It is estimated that it affects 8–16% of the adult population, generating high costs for health systems and high morbidity and mortality for patients, especially when it progresses to more advanced stages [17]. In recent decades, environmental and occupational factors have been associated with CKD. Among climate changes, rising temperatures and heat waves are the events that are expected to most affect both the occurrence of CKD and its worsening in those who already have it [18].

A recent study showed that the global burden of mortality from CKD attributable to high temperatures increased significantly between 1990 and 2019, particularly in tropical and subtropical regions with low-medium and low sociodemographic development indices [19]. A post hoc analysis of a study with more than 4000 people from 21 countries with pre-existing CKD showed a faster decline in the estimated glomerular filtration rate (eGFR) in those living in very hot climates compared to those living in temperate climates, an additional loss of 3.7 mL per 1.73 m^2/year in people with an eGFR of 45 mL per 1.73 m^2 [20].

3.3.1 Chronic Kidney Disease from Nontraditional Causes (CKDnt)

Repeated episodes of AKI resulting from exposure to heat stress (Fig. 3.2) have been proposed as a major etiological factor in CKD epidemics worldwide in warm climates, first documented in sugarcane harvesting populations in Central America [21, 22]. Although it has received other names, this global phenomenon has been called CKD of nontraditional origin (CKDnt) or CKD of unknown origin (CKDu), and it is a primarily tubulointerstitial disorder with nonproteinuric loss of renal function. The diagnosis is made when a patient meets the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for CKD without evidence of a recognized cause, such as diabetes, hypertension, genetic disease, or glomerulonephritis [23]. In addition to heat stress, exposure to other environmental and occupational factors, such as metals and pesticides, is being investigated as a possible contributor to CKDnt epidemics. It is likely that these and other factors interact with each other and that the etiology differs between different regions of the world [24]. Regarding the role of infectious diseases, as causal evidence, studies in the Americas have not yet found evidence [25, 26]. In Sri Lanka, the seroprevalence of hantavirus was higher in patients with CKD (40.6–60.0%) and healthy individuals in CKD-endemic areas (17.6–25.5%) than in healthy individuals in non-endemic areas (3.0%) [27]. Other investigations also suggest that exposure to *Leptospira* infection may be one of the possible causal factors of the disease in this same Asian country [28]. In the case of Central America, increasing evidence supports the hypothesis that chronic exposure to occupational heat stress is the main cause of the epidemic, locally named Mesoamerican nephropathy [26]. In a cohort of 569 workers in El Salvador and Nicaragua, decreased renal function was associated with higher body temperatures and heart rates in the workplace [29]. Furthermore, interventional research shows the benefits of hydration, shade, and rest programs in preventing renal dysfunction in workers at high risk of heat stress [30, 31], which reinforces the interaction between climate and occupation as direct agents of renal function impairment.

3.3.2 CKDnt in Brazil

In Brazil, CKD of unknown etiology is relatively high. According to the Brazilian Dialysis Surveys, which gathers information on patients undergoing dialysis treatment in approximately one-third of dialysis units, the primary cause of CKD in the last 5 years was unknown for 10–11% of patients [32]. Thus, it is very likely that CKDnt is a relevant cause of CKD, since a large part of the population is exposed to extreme heat condi-

tions, as well as to pesticides and metals [33–36]. Furthermore, the lack of adequate regulation and monitoring related to CKDnt risk factors, associated with the limited existence of public policies and strategies to detect and treat CKD, may increase the risk of workers developing the disease [37]. The effects of heat stress on renal function have been very little studied in Brazil. In two studies with a small number of participants that evaluated the acute effects of sugarcane harvesting activity on renal function, both found a significant difference in estimated glomerular filtration rate (eGFR) after the work shift [38, 39]. Similarly, in a pilot study that included industrial workers exposed (and not exposed) to heat stress and moderate physical exertion, it was found that those exposed had a greater decline in eGFR during the work shift [40]. However, after 2 years, there was no decrease in renal function compared to the first collection [41]. The better working conditions when compared to those experienced by rural workers (usually informal and paid for productivity), in addition to access to cooling, rest, and hydration areas, to the local occupational health service, and to the social security system protection network, may have protected the renal health of these industrial workers during the follow-up period.

With the increasing number of cases, high treatment costs, and significant impairment of the quality of life of those affected, strategies to mitigate the risk of CKD are extremely important. In the case of CKDnt, which especially affects young adults of working age, in addition to being preventable, it can benefit both employees and employers. A study that evaluated the productivity of almost 1300 sugarcane workers over 5 harvests in which increased rest time, shade, and hydration interventions were implemented found an increase in productivity despite the workers having reduced the number of hours they cut sugarcane [42].

It is known that CKDnt is a tubulointerstitial disorder, and in a large study conducted in the country that included daily data on hospital admissions from 1816 Brazilian cities between 2000 and 2015, the authors found that the increase in hospital admissions for renal tubulointerstitial diseases was associated with the increase in local temperature (17% for each 1 °C increase in average temperature) [5].

As an additional aggravating factor, Brazil has tropical and subtropical climates, being susceptible to atmospheric situations that favor extreme heat. The country is projected to face severe heat stress conditions by the end of this century as the effects of extreme warming materialize [43].

3.4 Lithiasis

Kidney stone formation, renal lithiasis, is a very common disease that causes a huge health-care burden among the working-age population [44]. It has a high incidence, with rates of 7–13% in North America, 5–9% in Europe, and 1–5% in Asia [45]. In the United States, the prevalence of self-reported kidney stones has nearly tripled, from 3.2% in 1976–1980 to 8.8% in 2007–2010 [46] and to 10.1% in 2014 [47]. Current trends show an increasing incidence of this disease worldwide, with an overall lifetime risk of 10% [45, 48]. Unfortunately, current scientific articles on the frequency of kidney stone episodes in Brazil are scarce [49], but according to the Brazilian Society of Urology (SBU), it is estimated that one in ten adults in Brazil has kidney stones throughout life and this number tends to increase [50].

Several hypotheses for this increase in the incidence and prevalence of kidney stones have been proposed, including the increasing prevalence of obesity, diabetes, gout, and changes in diet that affect urinary biochemical parameters. In addition to biological factors, demographic, economic, and environmental factors such as climate (including temperature and humidity levels), current climate change, and occupational factors have been associated with the increase in urolithiasis worldwide [47, 51–53].

For over a decade, a direct association has been observed between the climatic season of the year and a higher prevalence of stones and episodes of renal colic, including the number of hos-

pital admissions for treatment of lithiasis in the hottest months of the year [49]. In Brazil, the SBU reports that the incidence of lithiasis cases can increase by 30% in the summer. In other countries, Eisner et al. [54] and Ross et al. [55] also demonstrated a higher incidence of kidney stones in the summer.

In addition to the influence of the seasons, studies on the demographic and geographic variability of the incidence of lithiasis reveal higher rates of hospitalization in regions with warmer climates and lower rates in colder regions [55, 56]. In Brazil, higher rates of hospitalizations due to nephrolithiasis have been reported in cities with tropical climates, compared to cities with subtropical climates [57].

The main reason for this association between climate/temperature and lithiasis is due to the lower production of urine resulting from the excessive loss of fluids through sweat, without sufficient replacement through water consumption. This fact increases urinary saturation of stone-forming salts, promoting nucleation [56, 58].

In comparison to the general population, an increased risk of lithiasis of 4–20 times greater is also found in occupations in which workers are exposed to higher temperatures, such as lifeguards, workers in the glass and steel industries, and workers who perform outdoor tasks [59]. In a study conducted in Rio de Janeiro that included more than 10,000 workers in the steel industry, those who performed their duties in an area with high temperatures had a 9 times greater risk of lithiasis, compared to the group that remained in an area with room temperature [60].

The monitoring of North American military personnel who served in Southeast Asia showed that after arriving at the location and being exposed to high temperatures, the average time to seek hospital care due to symptomatic urinary stones was 93 ± 42 days [61].

3.4.1 Kidney Stones and Climate Change

In a national study, in addition to higher temperatures showing a significant association with increased hospitalizations, increased air humidity was associated with a decrease in hospitalizations for nephrolithiasis. According to these researchers, an increase in temperature in the presence of low humidity would be the worst-case scenario for people susceptible to the formation of kidney stones [57]. If these results are extrapolated to the Brazilian population, which according to IBGE data is made up of more than 200 million people [62], there will be approximately 592 new hospitalizations per month, or 7104 new hospitalizations per year, if there is a 1 °C increase in the average monthly temperature [57] (Fig. 3.3).

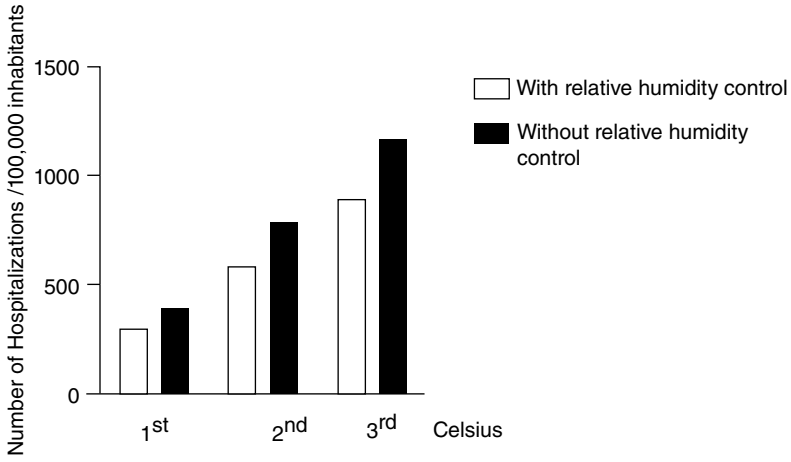


Fig. 3.3 Expected increases in hospitalizations for nephrolithiasis due to increases in global mean temperature, with and without relative humidity control, for a population of 100 million inhabitants [57]

A model of the impact of climate change on kidney stone formation reported that the fraction of the US population living in high-risk areas for kidney stones will increase from 40% to 56% by 2050 and to 70% by 2095. This is a projected increase of 1.6–2.2 million lifetime cases of kidney stones by 2050, increasing treatment costs by at least 25% [56].

3.5 Conclusions

Due to overlapping environmental and social risk factors, populations in developing countries are likely to be disproportionately affected by climate-related health impacts, including increased risk of kidney disease [63].

Mitigating climate-, environment-, and occupation-related kidney health impacts requires global, regional, local, and individual actions [64]. Global efforts include actions to reduce poverty and limit the consequences of climate change. Regional actions should include public education campaigns, as well as initiatives to regulate and monitor working conditions [37], while local actions should aim to improve occupational variables such as rest time and access to hydration. [64] At the individual level, self-monitoring, through regular observation of thirst, acute weight loss, and urine color, is a recommended tool to monitor hydration status [65].

The association between temperature and kidney problems is consistent and is likely to worsen with climate change. However, millions of future cases could be prevented by implementing joint actions to mitigate risk factors.

3.6 Take-Home Message

- Actions to minimize the impact of climate change on kidney health include:
  - Public campaigns to educate the population about the importance of maintaining good hydration throughout life through self-monitoring.
  - Reducing and adapting workplaces to reduce the risk of heat stress for workers.
  - Increasing awareness among people with kidney problems and those at greater risk of dehydration about the need to stay well hydrated.

References

1. WHO (World Health Organization). Climate change and health. https://www.who.int/news-room/fact-sheets/detail/climate-change-and-health. Accessed 9 Mar 2024.
2. Sasai F, Roncal-Jimenez C, Rogers K, et al. Climate change and nephrology. Nephrol Dial Transplant. 2023;38:41–8.
3. Barraclough KA, Blashki GA, Holt SG, et al. Climate change and kidney disease—threats and opportunities. Kidney Int. 2017;92:526–30.
4. Liu J, Varghese BM, Hansen A, et al. Hot weather as a risk factor for kidney disease outcomes: a systematic review and meta-analysis of epidemiological evidence. Sci Total Environ. 2021;801:149806.
5. Wen B, Xu R, Wu Y, et al. Association between ambient temperature and hospitalization for renal diseases in Brazil during 2000–2015: a nationwide case-crossover study. Lancet Reg Health – Am. 2022;6:100101.
6. Tögel F, Westenfelder C. Recent advances in the understanding of acute kidney injury. F1000Prime Rep. 2014;6:83.
7. Mehta RL, Cerdá J, Burdmann EA, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015;385:2616–43.
8. Kidney Disease Improving Global Outcomes (KDIGO). Clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:6.
9. Hajat S, Casula A, Murage P, et al. Ambient heat and acute kidney injury: case-crossover analysis of 1 354 675 automated e-alert episodes linked to high-resolution climate data. Lancet Planet Health. 2024;8:e156–62.
10. Chapman CL, Johnson BD, Parker MD, et al. Kidney physiology and pathophysiology during heat stress and the modification by exercise, dehydration, heat acclimation and aging. Temperature. 2021;8:108–59.
11. de Lorenzo A, Liaño F. Altas temperaturas y nefrología: a propósito del cambio climático. Nefrologia. 2017;37:492–500.
12. Young SE, Khoshnaw LJ, Johnson RJ. Climate and the nephrologist: the intersection of climate change, kidney disease, and clinical care. Clin J Am Soc Nephrol. 2023;18:411–7.
13. Romanello M, McGushin A, MacGuire FAS, et al. Monitoring climate change and child health: the case for putting children in all policies. J Paediatr Child Health. 2021;57:1736–40.

14. Calice-Silva V, Vieira MA, Raimann JG, et al. Saliva urea nitrogen dipstick – a novel bedside diagnostic tool for acute kidney injury. Clin Nephrol. 2014;2014(82):358–66.
15. Schlader ZJ, Hostler D, Parker MD, et al. The potential for renal injury elicited by physical work in the heat. Nutrients. 2019;11:2087.
16. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371:58–66.
17. Bharati J, Jha V, Levin A. The global kidney health atlas: burden and opportunities to improve kidney health worldwide. Ann Nutr Metab. 2020;76:25–30.
18. Johnson RJ, Sánchez-Lozada LG, Newman LS, et al. Climate change and the kidney. Ann Nutr Metab. 2019;74:38–44.
19. He L, Xue B, Wang B, et al. Impact of high, low, and non-optimum temperatures on chronic kidney disease in a changing climate, 1990–2019: a global analysis. Environ Res; 212. Epub ahead of print 2022. https://doi.org/10.1016/j.envres.2022.113172.
20. Zhang Z, Heerspink HJL, Chertow GM, et al. Ambient heat exposure and kidney function in patients with chronic kidney disease: a post-hoc analysis of the DAPA-CKD trial. Lancet Planet Health. 2024;8:e225–33.
21. Garcia P, Anand S. Unraveling the mysteries of CKD of uncertain etiology. Clin J Am Soc Nephrol. 2022;17:1269–71.
22. Courville K, Bustamante N, Hurtado B, et al. Chronic kidney disease of nontraditional causes in Central Panama. BMC Nephrol. 2022;23:275.
23. Gifford FJ, Gifford RM, Eddleston M, et al. Endemic nephropathy around the world. Kidney Int Rep. 2017;2:282–92.
24. Nayak S, Rehman T, Patel K, et al. Factors associated with chronic kidney disease of unknown etiology (CKDu): a systematic review. Healthc; 11. Epub ahead of print 2023. https://doi.org/10.3390/healthcare11040551.
25. Yih WK, Kulldorff M, Friedman DJ, et al. Investigating possible infectious causes of chronic kidney disease of unknown etiology in a Nicaraguan mining community. Am J Trop Med Hyg. 2019;101:676–83.
26. Wesseling C, Glaser J, Rodríguez-Guzmán J, et al. Chronic kidney disease of non-traditional origin in Mesoamerica: a disease primarily driven by occupational heat stress. Rev Panam Salud Publica/Pan Am J Public Heal. 2020;44:1–13.
27. Gamage CD, Nanayakkara S, Sarathkumara YD, et al. Hantavirus infection as a risk factor for chronic kidney disease of unknown aetiology (CKDu) and its prevalence in endemic areas of Sri Lanka since 2010 according to a retrospective serological analysis. J Med Microbiol; 71. Epub ahead of print 16 December 2022. https://doi.org/10.1099/jmm.0.001630.
28. Premarathne SS, Gamage C, Chandrajith R, et al. Leptospirosis: a potential culprit for chronic kidney disease of uncertain etiology. Nephron. 2023;147:510–20.
29. Petropoulos ZE, Keogh SA, Jarquín E, et al. Heat stress and heat strain among outdoor workers in El Salvador and Nicaragua. J Expo Sci Environ Epidemiol. 2023;33:622–30.
30. Wegman DH, Apelqvist J, Bottai M, et al. Intervention to diminish dehydration and kidney damage among sugarcane workers. Scand J Work Environ Health. 2018;44:16–24.
31. Bodin T, García-Trabanino R, Weiss I, et al. Intervention to reduce heat stress and improve efficiency among sugarcane workers in El Salvador: phase 1. Occup Environ Med. 2016;73:409–16.
32. Nerbass FB, Lima HdN, Thomé FS, et al. Brazilian dialysis survey 2021. Brazilian J Nephrol. Epub ahead of print 4 November 2022. https://doi.org/10.1590/2175-8239-jbn-2022-0083en.
33. Bitencourt DP, Alves L, Shibuya EK, et al. Climate change impacts on heat stress in Brazil—past, present, and future implications for occupational heat exposure. Int J Climatol. 2021;41:E2741–56.
34. Goncalves AC, Nacke H, Schwantes D, et al. Heavy metal contamination in Brazilian agricultural soils due to application of fertilizers. In: Soriano M, editor. Environmental risk assessment of soil contamination. InTech. Epub ahead of print 26 March 2014. https://doi.org/10.5772/57268.
35. Buralli RJ, Ribeiro H, Iglesias V, et al. Occupational exposure to pesticides and health symptoms among family farmers in Brazil. Rev Saude Publica. 2020;54:1–12.
36. Carneiro FF (Org.), Augusto LGS, Rigotto RM, et al. Dossiê ABRASCO: um alerta sobre os impactos dos agrotóxicos na saúde. São Paulo, Brasil: Expressão Popular, 2015. Epub ahead of print 2015. https://doi.org/10.1016/B978-84-458-2066-7.00003-3.
37. Buralli RJ, Albuquerque PLM, Santo CE, et al. Occupational risks associated with chronic kidney disease of non-traditional origin (CKDnt) in Brazil: it is time to dig deeper into a neglected. Braz J Nephrol. Epub ahead of print 2024. https://doi.org/10.1590/2175-8239-JBN-2023-0123en
38. Paula Santos U, Zanetta DMT, Terra-Filho M, et al. Burnt sugarcane harvesting is associated with acute renal dysfunction. Kidney Int. 2015;87:792–9.
39. McKenna ZJ, Nava RC, Magalhães C, et al. A comprehensive evaluation of heat stress and heat strain in a sample of sugarcane cutters in Brazil. J Appl Physiol. 2023;135:1431–9.
40. Nerbass FB, Moist L, Clark WF, et al. Hydration status and kidney health of factory workers exposed to heat stress: a pilot feasibility study. Ann Nutr Metab. 2019;74:30–7.
41. Nerbass FB, Moist L, Vieira MA, et al. Kidney function in factory workers exposed to heat stress. J Occup Environ Med. 2022;64:e685–9.
42. Hansson E, Jakobsson K, Glaser J, et al. Impact of heat and a rest-shade-hydration intervention program on productivity of piece-paid industrial agricultural workers at risk of chronic kidney disease of nontraditional origin. Ann Work Expo Heal. Epub ahead

of print 17 February 2024. https://doi.org/10.1093/annweh/wxae007.
43. Hacon SS, Oliveira BFA, Silveira I. A review of the health sector impacts of 4 °C or more temperature rise. In: Nobre CA, Marengo JA, Soares WR, editors. Climate change risks in Brazil. Cham; 2019. p. 67–129.
44. Lu J, Hong D, Wu Q, et al. Association between urinary cobalt exposure and kidney stones in U.S. adult population: results from the national health and nutrition examination survey. Ren Fail. 2024;46:46.
45. Sorokin I, Mamoulakis C, Miyazawa K, et al. Epidemiology of stone disease across the world. World J Urol. 2017;35:1301–20.
46. Khan SR, Pearle MS, Robertson WG, et al. Kidney stones. Nat Rev Dis Prim. 2016;2:16008.
47. Chen Z, Prosperi M, Bird VY. Prevalence of kidney stones in the USA: the national health and nutrition evaluation survey. J Clin Urol. 2019;12:296–302.
48. Rukin NJ, Siddiqui ZA, Chedgy ECP, et al. Trends in upper tract stone disease in England: evidence from the hospital episodes statistics database. Urol Int. 2017;98:391–6.
49. Korkes F, Silva JL d II, Heilberg IP. Costs for in hospital treatment of urinary lithiasis in the Brazilian public health system. Einstein (São Paulo). 2011;9:518–22.
50. Sociedade Brasileira de Urologia. https://portaldaurologia.org.br/. Accessed 5 Apr 2024.
51. Buttigieg J, Attard S, Carachi A, et al. Nephrolithiasis, stone composition, meteorology, and seasons in Malta: is there any connection? Urol Ann. 2016;8:325.
52. Daudon M, Doré JC, Jungers P, et al. Changes in stone composition according to age and gender of patients: a multivariate epidemiological approach. Urol Res. 2004;32:241–7.
53. Thongprayoon C, Krambeck AE, Rule AD. Determining the true burden of kidney stone disease. Nat Rev Nephrol. 2020;16:736–46.
54. Eisner BH, Sheth S, Herrick B, et al. The effects of ambient temperature, humidity and season of year on urine composition in patients with nephrolithiasis. BJU Int. 2012;110:2–5.
55. Ross ME, Vicedo-Cabrera AM, Kopp RE, et al. Assessment of the combination of temperature and relative humidity on kidney stone presentations. Environ Res. 2018;162:97–105.
56. Brikowski TH, Lotan Y, Pearle MS. Climate-related increase in the prevalence of urolithiasis in the United States. Proc Natl Acad Sci. 2008;105:9841–6.
57. Abreu Júnior J d, Ferreira Filho SR. Influence of climate on the number of hospitalizations for nephrolithiasis in urban regions in Brazil. Braz J Nephrol. 2020;42:175–81.
58. Soucie JM, Coates RJ, McClellan W, et al. Relation between geographic variability in kidney stones prevalence and risk factors for stones. Am J Epidemiol. 1996;143:487–95.
59. Nerbass FB, Pecoits-Filho R. Can your work affect your kidney's health? Rev Environ Health. 2019;34:441–6.
60. Atan L, Andreoni C, Ortiz V, et al. High kidney stone risk in men working in steel industry at hot temperatures. Urology. 2005;65:858–61.
61. Evans K, Costabile RA. Time to development of symptomatic urinary calculi in a high risk environment. J Urol. 2005;173:858–61.
62. Instituto Brasileiro de Geografia e Estatística. https://censo2022.ibge.gov.br/panorama/. Accessed 16 Jan 2024.
63. Freidin N, Hayes E, Struthers SA. Implications of climate change on acute kidney injury. Curr Opin Nephrol Hypertens. 2024;33:83–8.
64. Nerbass FB, Pecoits-Filho R, Calice-Silva V. The environmental role of hydration in kidney health and disease. In: Contributions to nephrology. Basel: Karger. p. 252–65.
65. Cheuvront SN, Kenefick RW. Am I drinking enough? Yes, no, and maybe. J Am Coll Nutr. 2016;5724:1–8.

Part II

Kidney Diseases Associated to Environmental Factors and Exogenous Agents

4 Environmental Factors Causing Kidney Diseases

Edgar Sanclemente-Paz, David Ballesteros, and Giovanni Apraez

4.1 Introduction

The environment has undergone a dangerous transformation with the introduction of hundreds of thousands of synthetic chemical substances, not always harmless and eventually harmful to the health of living beings. We are in the presence of a true "chemical pandemic."

The kidney, in this context, being a route of excretion of compounds foreign to the organism, is the target organ par excellence to receive the impact of toxins in its structures [1].

Environmental toxins induce endoplasmic reticulum stress, mitochondrial dysfunction, and oxidative stress, with excessive production of reactive oxygen species that lead to apoptosis, cellular necrosis, and eventually progressive kidney injury [2].

It has been identified that atmospheric pollution can induce an inflammatory response by the release of interleukins (IL-6, IL-1β) and TNF-α and oxidative stress. The result is vascular injury with platelet activation and thrombin generation by adhesion molecules, leading to a prothrombotic state [3].

Toxic substances are producing alterations in kidney functions that can induce acute kidney injury and contribute to the development of chronic kidney disease and also have an influence on risk factors such as hypertension and diabetes mellitus.

The alarming environmental pollution (biological, physical, and chemical) tends to be worldwide, and environmental pollution by heavy metals and other toxic substances has been evidenced in most countries around the globe. However, Latin America and Asia exhibit high rates [4].

Environmental pollution is being considered more strongly as a contributing factor in the appearance of CKD and its risk factors such as diabetes, hypertension, obesity, and metabolic syndrome [5].

Environmental, occupational, and intramural toxic nephropathy has not received sufficient attention to date as a contributing agent in the origin of chronic kidney damage. Currently, "green spaces," contact with lush vegetation without environmental pollution, are being considered as an important contributing factor in kidney health and its risk factors [6].

Endocrine disruptors in the environment, harmful substances that interfere with the synthesis of hormones and metabolism in general, are apparently involved in the development of obe-

E. Sanclemente-Paz (✉)
Department of Internal Medicine, Faculty of Medicine, University of Cauca, Popayán, Cauca, Colombia
e-mail: esanclemente@imbanaco.com.co

D. Ballesteros
Departamento de Medicina Interna, Facultad de Ciencias de la Salud, Universidad del Cauca, Popayán, Cauca, Colombia

G. Apraez
Departamento de Salud Pública, Facultad de Medicina, Universidad Nacional de Colombia, Bogota D.E., Colombia

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_4

sity and diabetes, risk factors for chronic kidney disease [7].

Global warming secondary to the loss of the ozone layer, increasing ambient temperature, together with toxins (heavy metals) and dehydration, is an important factor in the development of chronic kidney damage [8–10].

4.2 Environmental Pollution and Risk Factors for Kidney Disease

High blood pressure, as a risk factor for CKD, is increasing in most communities and is increasingly affecting younger and more working-age people. Noise, in the modern era, seems to be one of the risk factors for this pathological entity. Air pollution by 2.5 micron particles and nitrogen oxide may be another important cause for the development of high blood pressure, due to its ability to induce the inflammatory phenomenon, both in adults and children. Exposure to environmental chemicals, such as dioxins, bisphenol, phthalates, DEP (diesel exhaust particulate matter), PFAS, and PAH (polycyclic aromatic hydrocarbons), are related to the onset of high blood pressure. Excess heavy metals (As, Cd, Pb, Hg) accumulated in the body are linked to HBP. Lead, cadmium, and mercury contamination may be related to arterial hypertension resistant to hypotensive medication [11–14].

4.3 Obesity and Diabetes Mellitus

Diabetic kidney disease is a frequent complication and is characterized by elevated albumin excretion in urine and a persistent decrease in the glomerular filtration rate, frequently accompanied by arterial hypertension (90%). However, albuminuria is not a requirement for diagnosis, since, in a small number of patients with biopsy-proven diabetic nephropathy, elevated levels of albumin in urine are not present, but a decrease in the glomerular filtration rate and its progression to chronicity is much greater [15–19].

In the CRIC study (chronic kidney disease biomarkers study and cohort of kidney failure researchers), the determination of plasma indicators of the risk of progression of diabetic nephropathy showed that elevated levels of KIM-1, TNRF-1, TNRF2, MCP-1, suPAR, and YKL-40 are associated with a greater progression of chronic kidney injury [20–23].

Air pollution by PM2.5 and PM10 appears to be an important cause for the development of DM. Some toxic substances, derived from plastics, such as bisphenol A, phthalates, and polycyclic aromatic hydrocarbons, in addition to air pollution (NO_2) and vehicular traffic, apparently acting as endocrine disruptors, are involved in insulin resistance, pre-diabetes, diabetes, and metabolic syndrome. Arsenic, lead, cobalt, strontium, uranium, and cadmium have been linked to the onset of diabetes mellitus [24–30].

4.4 Environmental Pollution and Kidney Damage

Acute kidney injury is the common denominator for most nephrotoxic agents and is caused by exposure to heavy metals such as mercury, lead, cadmium, uranium, chromium, vanadium, antimony, solvents, pesticides, and other chemical compounds and can be an important risk factor for the development of chronic kidney disease and its progression.

One of the risk factors for the development of chronic kidney disease is having suffered acute kidney injury due to an incomplete tubular repair process after the acute episode. The immunological reaction, with the persistence of macrophages after tubular damage, induces an inflammatory response that can lead to progressive interstitial fibrosis by the secretion of profibrotic cytokines (TGF-beta, CTGF), activation of pericytes with generation of myofibroblasts, destruction of peritubular capillaries, inflammation, and production of extracellular matrix [31]. Approximately 20% of patients who have suffered acute kidney injury may exhibit long-term chronic kidney disease; therefore, it is advisable to monitor this type of kidney pathology in them [32].

4.4.1 Transition between Acute Kidney Injury and Chronic Renal Disease

In response to toxic injury, tubular cells synthesize and secrete a series of bioactive molecules that lead to inflammation and subsequent fibrosis. The mechanisms involved are irreversible cell damage by hypoxia, secretion of profibrotic cytokines, generation of myofibroblasts, inflammatory phenomena, mitochondrial dysfunction, injury to peritubular capillaries, and production of extracellular matrix. The immune response resulting from acute kidney injury is innate and adaptive in nature, contributing to the transition from acute to chronic kidney injury and its progression [33].

The initial renal damage from most nephrotoxic agents is acute kidney injury, which compromises tubulointerstitial structures with tubular necrosis or acute interstitial nephritis, which generally recovers completely, especially if the injury and impairment of function are mild or moderate. However, there are a significant number of clinical situations, with severe or longer-lasting damage, in which renal damage progressively progresses to chronic renal injury with interstitial and glomerular fibrosis and vascular involvement [34].

4.4.2 Chronic Kidney Disease

It is a complex disease that affects between 8% and 16% of the world's population, and developing countries have high prevalence rates. It is estimated that approximately 850 million people in the world suffer from chronic kidney disease, with an incidence of approximately 12%, depending on the geographic region, ethnic group, and age. This pathological entity has increased worldwide. It is a pathological condition that constitutes a growing public health problem in the world and represents a high-cost disease due to the need for replacement therapies. Chronic kidney disease is a direct cause of global morbidity and mortality, in addition to being a risk factor for cardiovascular diseases [35, 36].

The prevalence of chronic kidney disease in most countries of the world has been increasing in a worrying manner. It is estimated that 13% of people suffer from some degree of chronic kidney injury. The prevalence is higher in women (11.8%) and in Afro-descendants (16.5%) and increases linearly with age with 27.9% between 70 and 80 years [37, 38].

According to the latest international report, in South America, countries such as Brazil and Colombia are among the 12 countries in the world in which the prevalence of chronic kidney disease in treatment and dialysis has increased between 2009 and 2019 [38].

The major risk factors in the world for chronic kidney disease include diabetes mellitus and arterial hypertension. To a lesser extent, primary kidney diseases (glomerulonephritis and interstitial nephritis) and those of a hereditary nature are observed. However, in up to 30%, the cause of this pathological entity is unknown, and in some cases, it is endemic in nature [39].

Since there is a significant proportion of chronic kidney diseases whose cause is unknown, it can be assumed that one of the important factors that are influencing their appearance and progression is of a toxic-environmental nature, such as heavy metals. Chronic kidney disease is defined as the presence of kidney damage or decreased kidney function for 3 months or more, regardless of the cause. A decrease to levels below 60 mL/min/1.73 m^2 is considered indicative of chronic kidney disease, and levels below 15 mL/min/1.73 m^2 are defined as kidney failure and require renal replacement therapy (dialysis) or kidney transplant.

Kidney dysfunction refers to a decrease in the glomerular filtration rate (GFR), which is determined by serum creatinine (using a properly calibrated method), using various equations to calculate it (eGFR). It has been established that the formula called CKD-EPI is more accurate in calculating the glomerular filtration rate [40, 41].

Substantial and significant discrepancies have been seen with the use of the calculated filtration rate based on creatinine because of its large variability using the various existing formulas and the albumin-creatinine ratio in different ethnic groups [42–44].

The two urine tests commonly used in clinic to predict 24 hours protein excretion are UPCR (urine protein to creatinine ratio) and UACR (urine albumin to creatinine ratio), which are used as indicators of renal injury and the effectiveness of treatments, as well as a prognostic factor. However, these determinants are limited by the fact that urinary creatinine can be very variable even within the same day. In addition, urinary protein excretion also has a lot of variability over time and on a daily basis [45].

In proximal tubule injury, some of the heavy metals such as cadmium, arsenic, lead, chromium, nickel, and mercury prevent albumin reabsorption, and there may be significant microalbuminuria without being related to glomerular injury [46].

When there is chronic tubular injury, the measurement of the glomerular filtration rate calculated on the basis of serum creatinine is a late marker and correlates very poorly with tubulointerstitial fibrosis, a crucial pathological lesion in the progression of kidney disease of any cause.

In early interstitial kidney damage, renal injury biomarkers such as KIM-1 are required, which could detect early subclinical situations of chronic kidney disease, hence its usefulness in the progression of chronic kidney disease induced by nephrotoxins [47, 48].

Chronic kidney disease is heterogeneous, and the role of genetics, which is highly influential in conjunction with environmental factors, has been little considered in the etiological diagnosis. Recent research has shown that 10% of adults and 20% of children have genetic variants related to the cause of chronic kidney disease, according to a state-of-the-art gene panel [49, 50].

Nephropathy of environmental toxicity due to air pollution, heavy metals, agrochemicals, solvents, and aristolochic acid should be considered as a cause of chronic kidney disease, especially in Latin America [4, 12, 51–54]. A type of chronic kidney disease has been described in the world literature, the origin of which is unknown, independent of traditional causes, and which mainly affects sugarcane cutters, but also corn and cotton farmers, brickyard workers, and road construction workers in Central America (El Salvador, Nicaragua, Guatemala, Mexico, Costa Rica, and Panama), as well as agricultural workers in Sri Lanka, Egypt, India, Tunisia, Paraguay, and Australian aborigines. It is very likely that this pathological entity exists in other South American countries.

It is characterized by chronic tubulointerstitial lesions. Hypovolemia with subclinical and repetitive episodes of acute kidney injury, heavy metals (Cd, Pb, As, and W), pesticides (paraquat, glyphosate), agrochemicals, aristolochic acid, mycotoxins, infectious agents, non-steroidal anti-inflammatory drugs, and genetic factors, among others (APOL1, UMOD), have been speculated about its cause. Kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and metallothionein 2A (MT2A) are important biomarkers in the diagnosis and prognosis of chronic kidney disease of unknown origin [55–66] (Fig. 4.1).

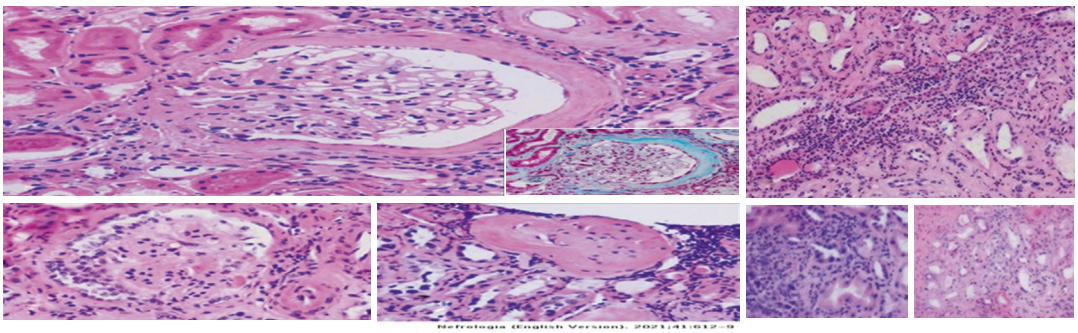


Fig. 4.1 Mesoamerican nephropathy. Pericapsular fibrosis—sclerosis; fibrosis and interstitial tubular atrophy; fibrosis of the glomeruli; infiltration by lymphocytes. (Adapted from Valldivia Mazeira M et al. *Nefrologia*; 2022 41: 612–619)

4.4.3 Pathophysiology of Nephrotoxicity

Toxic nephropathies, both endogenous and exogenous, are a group of kidney diseases characterized by lesions affecting the tubulointerstitial area, glomeruli, and vessels, which can contribute to the development of chronic kidney damage.

Most toxic substances, including heavy metals, are filtered through the glomerulus and reabsorbed in the tubules, mainly in the proximal ones, which are particularly vulnerable, inducing acute kidney injury, which can be associated with the development of chronic kidney damage, when the repair of renal tissue is not optimal and can contribute to progressive interstitial fibrosis.

The subclinical inflammatory phenomenon is a basic process in chronic kidney injury and is part of the progression of the disease, in which fibrosis, its primary factor, is the stimulation of transforming growth factor beta (TGF-β). It is a determining process characterized by the proliferation of fibroblasts and an increase in the extracellular matrix and inhibition of its degradation in the glomeruli and in the renal interstitium [67, 68].

Kidney fibrosis, especially tubulointerstitial fibrosis, is a chronic and progressive process that affects the renal structures including the glomeruli, regardless of the cause, and is the inevitable consequence of the progress of all chronic kidney diseases.

The histopathological picture consists of interstitial fibrosis with infiltration of mononuclear cells, periglomerular fibrosis, tubular atrophy and dilatation, accumulation of extracellular matrix, and hyalinosis of the vessels (Fig. 4.2).

Chronic exposure to toxic substances causes chronic tubulointerstitial injury with subsequent compromise of the glomeruli and vessels that may go unnoticed until they lead to irreversible renal damage, without being detected by traditional markers.

For this reason, in nephropathy of environmental toxicity and other causes, it is necessary to consider markers that indicate incipient tubular damage and that unfortunately have been ignored in renal prevention programs. For entities that allocate funds for health research, chronic kidney disease due to nephrotoxins is a practically invisible pathological condition [69, 70].

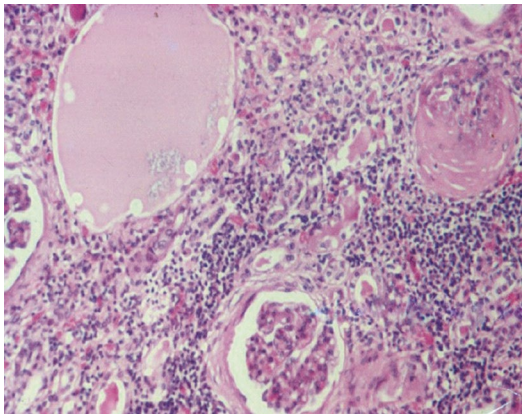


Fig. 4.2 Chronic tubulointerstitial nephritis. Capsular fibrosis-glomerular sclerosis; atrophy and tubular dilatation—lymphocyte infiltration. (Images by Dr. Edgar Sanclemente, MD)

Traditional methods such as creatinine and proteinuria do not adequately synchronize with the magnitude of renal damage and are not sensitive enough to identify the progression of chronic kidney disease and thus improve its prognosis by early intervention in the process [71].

Inflammatory biomarkers such as cytokine TNFα and its receptors (TNRF-1 and TNRF-2), monocyte chemotactic protein 1 (MCP-1), cell adhesion molecules (CAMs), kidney injury molecule-1 (KIM-1), chemokines, and other markers play a very important role in the development and progression of fibrosis in chronic kidney disease [72].

Biomarkers of fibrosis and disease progression are determinants of chronic kidney injury. The most commonly used are metalloproteinases (MMPs), Dickkof-3 (DKK-3), galectin-3 (GAL-3), epithelial growth factor (EGF), soluble urokinase-type plasminogen activator receptor (suPAR), fibroblast growth factor 23 (FGF23), uromodulin (UMOD), and Klotho, among the main ones [73, 74].

4.5 Environmental Pollution and Nephrotoxicity

Air pollution is a complex mixture of gases, solid components, and liquids suspended in air. Particulate matter is composed of solid particles (PM10 and PM2.5) that come from the combustion of coal, gasoline, and diesel. Additional gaseous components are NO_2, CO, SO_2, and O_3 and heavy metals Hg, Cd, and Pb. There is evidence that environmental pollution is a risk factor for chronic kidney injury [75–78].

It is speculated that air pollution may initiate from the release of inflammatory mediators in the lung, which pass into the circulation, and induce oxidative stress and a systemic inflammatory phenomenon that compromises the kidney and other organs [79].

In Asian children and adolescents, it was observed that air pollution with PM2.5 and NO_2 particles was associated with a decrease in the glomerular filtration rate and an increased risk of developing chronic kidney disease. In children, exposure to air polluted with sulfur dioxide, hydrocarbons, and methane is associated with an increased incidence of idiopathic nephrotic syndrome [80, 81].

Research in some countries showed that long-term exposure to 2.5 micron particulate matter (PM2.5) is associated with the risk of suffering from some types of glomerulonephritis and membranous nephropathy [82].

A study in children revealed that exposure to high temperatures and 2.5 micron fine particulate matter (PM2.5) is associated with an increase and decrease in some biomarkers of renal damage, indicating incipient glomerular and tubular injury [83].

Studies in the adult population of several countries showed that air pollution with PM10, PM2.5, SO_2, and NO_2 particles is associated with albuminuria, a decrease in the calculated glomerular filtration rate, a high prevalence of chronic kidney disease, and an increased risk of its progression [84–92].

Several investigations with systematic reviews in different countries of the world describe an association between fine particles of 2.5 microns and other components in the environment, with the risk of suffering from chronic kidney disease [93–96].

Long-term exposure to ozone (O_3) decreases the glomerular filtration rate and constitutes a risk for the development of chronic kidney disease and increases mortality from this cause [97, 98].

Environmental pollution is also associated with risk factors for developing chronic kidney disease, high blood pressure, diabetes mellitus, obesity, and metabolic syndrome [99–101].

Air pollution increases the risk of end-stage renal disease in patients with type 2 diabetes with chronic kidney disease due to diabetic nephropathy [102].

4.6 Heavy Metal Nephrotoxicity

Recent studies indicate that heavy metals produce oxidative stress, with the generation of reactive species, which is the basis of cellular damage including apoptosis, endoplasmic reticulum, and mitochondrial stress, and exacerbate the inflammatory process [103, 104].

Occupational and environmental exposures to multiple heavy metals are one of the major risks for nephrotoxicity, and therefore, their early identification is very important for prevention and treatment.

Some heavy metals are nephrotoxic; frequently alter tubular function, affecting the reabsorption of electrolytes, amino acids, and low molecular weight proteins; and can cause acute and chronic tubulointerstitial nephritis. They eventually compromise the glomeruli, producing a decrease in the glomerular filtration rate and sometimes nephrotic syndrome with massive albuminuria [105].

Iron deficiency, a common occurrence in malnourished and low-income individuals and in chronic kidney patients, can increase the damage caused by nephrotoxic heavy metals [106].

A systematic review and meta-analysis revealed that exposure to cadmium, lead, and arsenic may increase the risk of developing chronic kidney disease [107, 108].

The combination of polyfluoroalkyl compounds (PFAS) with Hg and Cd is associated with decreased glomerular filtration rate according to a study in the United States [109].

Low levels of cadmium and lead are associated with a higher prevalence of chronic kidney disease, according to a study in the adult population of the United States [110, 111].

Patients with chronic kidney disease are very susceptible to exposure to nephrotoxic heavy metals even at low concentrations [112, 113].

Older people are more susceptible to decreased glomerular filtration rate due to exposure to the mixture of potentially nephrotoxic heavy metals [114].

Exposure to cadmium, arsenic, and glyphosate may be a risk factor for the progression of chronic kidney disease [115]. Heavy metals such as cadmium, arsenic, and lead are associated with hyperuricemia, a risk factor for chronic kidney disease, according to a study in the general population of the United States [116, 117].

Exposure to some xenobiotics such as silica, mercury, asbestos, and solvents is associated with induced autoimmunity and autoimmune diseases (SLE) [118].

Exposure to some metals (Cd, Pb, Cu, Co, and U) and other toxic substances is linked to the onset of diabetes mellitus and therefore to diabetic nephropathy [30, 119–121].

It appears that elevated blood levels of selenium, due to its antioxidant effect, and zinc, which maintains the levels of metallothioneins that prevent damage caused by free radicals, can counteract the effect of nephrotoxic metals and provide some protection against developing chronic kidney disease [122].

4.7 Biomarkers of Heavy Metal Nephrotoxicity

Common and universally accepted markers such as creatinine, urea nitrogen, and urinary albumin-creatinine ratio are insensitive and specifically inadequate for the diagnosis and prognosis of tubulointerstitial lesions due to nephrotoxicity of metals, metalloids, and other toxic substances.

Biomarkers such as β2-microglobulin (β2-MG), N-acetyl-β-D-glucosaminidase (NAG), kidney injury molecule-1 (KIM-1), neutrophil lipocalin-associated gelatinase (NGAL), urinary retinol-binding protein (RBP), metallothioneins (MT1A and MT2A), and uromodulin (Tamm-Horsfall protein) are indicated for the diagnosis and prognosis of renal lesions caused by nephrotoxic agents, including heavy metals. Other less used markers and some of them under research in heavy metal nephrotoxicity are α1-microglobulin, α-glutathione-transferase, and γ-glutamyl-transpeptidase [123–125].

4.8 Mercury

All forms of mercury are toxic to humans, but methylmercury is especially toxic. Renal nephrotoxicity is more dependent on the ingestion of contaminated food, mainly fish and water, than on inhalation of mercury vapors [126].

Mercury contamination in the Amazon is a cause for concern, due to water pollution from artisanal mining. Most inhabitants of the Brazilian border city of Santarém exhibit elevated levels of mercury, especially in people between 40 and 60 years of age [127].

Some types of traditional Chinese and Indian medicines (Ayurvedic), skin-lightening creams, and hair-dyeing substances may contain significant levels of mercury [128].

Accumulation of mercury in the kidney causes acute kidney injury with necrosis and damage to the distal and middle portion of the proximal tubule by inhibition of protein synthesis and mitochondrial injury. There are studies that relate the increased susceptibility to Hg poisoning with some genes such as those of the glutathione system and ATP binding with metallothionein transporters. According to a recent study, exposure to mercury induces damage to the cytoskeleton and loss of renal function through an epigenetic modulation of the expression of metalloproteinase 9. The proximal tubule injury due to mercury is linked to the decrease of thiol radicals at the cellular level leading to oxidative stress [129, 130].

Mercury, even at low concentrations, can produce tubular injury, characterized by increased excretion of albumin, transferrin, retinol-binding protein, α1-microglobulin, β2-microglobulin, galactosidase, and N-acetyl-β-D-glucosaminidase (NAG), which is very useful to detect early nephrotoxicity due to Hg at low concentrations in chronic occupational exposure [131].

Nephrotic syndromes due to minimal change disease, focal segmental sclerosis, and membranous glomerulopathy have been described in association with the use of skin depigmentation creams and hair dyes, ingestion of Ayurvedic medicines and Chinese herbal therapy contaminated with Hg, psoriasis treatments, and occupational exposure. Chelation and, if appropriate, steroids are the ideal treatment [132–137] (Fig. 4.3).

There is no evidence that long-term exposure to mercury is associated with chronic kidney disease, but it may be a risk factor and cause mortality.

In Ghana and Indonesia, gold miners in small-scale artisanal mines without adequate protection have been found to have elevated blood mercury concentrations, decreased filtration rates, and increased urinary protein [138, 139].

A study in Colombia of artisanal miners exposed to mercury vapor showed that low and moderate concentrations of Hg in blood (3.4–11 μg/L) and urine (1.3–9.6 μg/g creatinine) had no effect on glomerular filtration rate, calculated from serum creatinine, albumin excretion, and tubular function measured with β2-microglobulin [140].

In Colombia, among the most important communities of small-scale artisanal gold miners, it has been observed that the deterioration of renal function in artisanal mining is determined more by exposure to a mixture of heavy metals such as Cd, Pb, As, Be, and Mn than to them individually [141].

The kidney, in old age, is more sensitive to mercury exposure and therefore to its nephrotoxicity. In elderly patients, chronic exposure to

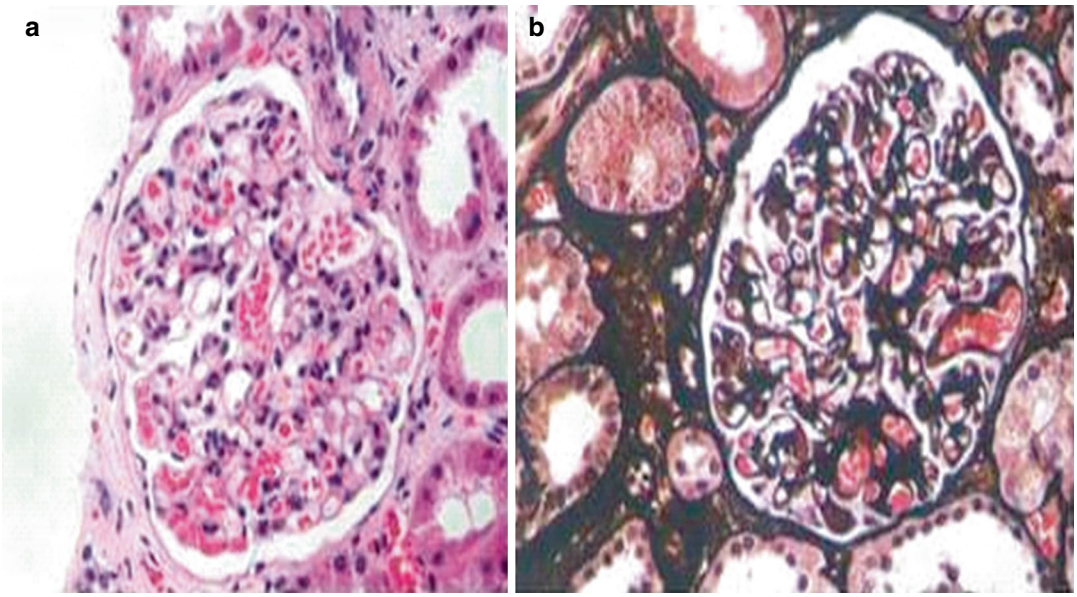


Fig. 4.3 (**a**) Mercury nephropathy—membranous glomerulopathy. (**b**) Thickening of the glomerular basement membrane. (Adapted by Doshi M et al. [133])

mercury can accelerate age-related nephropathy [142].

A recent systematic review and meta-analysis study carried out in Canada revealed a positive association between different concentrations of mercury in hair and arterial hypertension [143].

Mercury, in its organic and inorganic forms, is associated with autoimmunity according to a recent systematic review. An interesting fact is the relationship between methylmercury levels in blood and hair with the appearance of ANA test positive in women of reproductive age. The relationship between mercury exposure and autoimmune diseases such as systemic lupus erythematosus, with positive ANA autoantibodies, has recently been described [144].

4.9 Cadmium

Cadmium is a metal that occurs naturally in the earth's crust in combination with zinc and lead. It is bioaccumulative and persistent in the environment and is transported over long distances by wind and water.

Smoking is one of the factors that allows cadmium to enter the body. The Cd content per cigarette is 1–2 μg. A decrease in the glomerular filtration rate and an increase in microalbuminuria have been observed among apparently healthy smokers. It is presumed that there is potential chronic renal damage due to cadmium from cigarette smoking [145–148].

It binds to albumin, is metabolized in the liver by conjugation with metallothionein (MT), and then passes into the blood. It is eliminated by glomerular filtration and is absorbed in the proximal tubule by endocytosis through the megalin/cubilin complex. The Cd-MT molecule is degraded, releasing highly toxic cadmium ions into the cytosol, thus generating oxidative stress and causing cell death [149].

The mechanisms of cadmium, arsenic, and mercury toxicity at the renal level are linked to oxidative stress of the endoplasmic reticulum, DNA damage, and mitochondrial dysfunction leading to apoptosis and death of proximal tubule cells [150].

Excessive production of reactive oxygen species leading to a decrease in antioxidant defense systems, an increase in lipid peroxidation, and endothelial dysfunction has been described in exposed individuals with high blood levels of Cd [73, 151, 152]. Exposure to even low levels of cadmium, whether by inhalation or ingestion, is linked to tubular damage by apoptosis and oxidative stress, with loss of glucose, amino acid, and phosphate reabsorption (Fanconi syndrome), hypercalciuria, hyperphosphaturia, renal tubular acidosis, and increased excretion of tubular proteins such as β2-microglobulin, α1-microglobulin, and retinol-binding protein (RPB) [153, 154].

In patients with anemia, malnutrition, diabetes, and hypertension, cadmium toxicity is greater even with low exposures. Zinc and selenium, due to their antioxidant action, provide a renal protection effect. The biological half-life of cadmium in the kidney is 10–20 years, and this explains why cadmium continues to accumulate in humans after age 50, which is why prolonged exposure to cadmium exacerbates the decline in glomerular filtration rate associated with advancing age.

Chronic exposure to cadmium and elevated urinary excretion are associated with a marked decrease in glomerular filtration rate and may be a risk factor for the development of chronic kidney disease [155].

Chronic kidney injury from cadmium has been described with different levels of exposure in several countries: Belgium, Sweden, France, England, Poland, Czech Republic, the United States, India, Japan, China, and Mexico. However, a systematic review found no relationship between cadmium exposure in workers and in the general population and the progression of chronic kidney disease [156, 157].

According to a recent study, it has been documented that cadmium levels in the environment in many industrialized countries increase the risk of kidney injury and may contribute to the development of chronic kidney disease [158].

Several investigations have demonstrated an inverse association between the calculated filtration rate and blood levels of cadmium and a positive relationship between albuminuria and urinary cadmium, apparently due to reduction of the receptor that promotes endocytosis for the reabsorption of albumin and other proteins. It is documented that exposure to high levels of cadmium through ingestion increases the risk of chronic kidney disease and its progression [159–161].

In a recent study, in 222 sugarcane harvesters in Guatemala, an inverse relationship was observed between urinary cadmium and arsenic levels and the glomerular filtration rate calculated on the basis of creatinine and a positive association with the concentration of neutrophil gelatinase associated with lipocalin (NGAL) [162].

Biomarkers of renal injury due to cadmium, even at low doses, include increased urinary total protein excretion and albumin, β2-microglobulin, α1-microglobulin, kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), uromodulin (Tamm-Horsfall protein), and retinol-binding protein (RPB). [163–166].

Blood cadmium levels are the best index of recent exposure and in urine (cadmium/creatinine ratio) in patients over 60 years of age.

Kidney injury consists of interstitial fibrosis, tubular atrophy with or without mononuclear cell infiltration, sclerosis, and glomerular collapse. In addition, fibrosis and hyalinosis of the arteriolar intima layer are observed (Fig. 4.4).

Cadmium contamination, as deduced from research, is also related to risk factors for chronic kidney disease such as arterial hypertension, diabetes mellitus, and renal lithiasis [167–169].

A recent systematic review on the impact of environmental exposure to cadmium revealed a relationship with type 2 diabetes mellitus. Several meta-analyses have found a significant association between urinary cadmium levels and the risk of diabetes mellitus. Epidemiological studies have suggested a positive association between environmental exposure to cadmium on the incidence and severity of diabetes. Exposure to cadmium produces greater nephrotoxicity in diabetic patients [170].

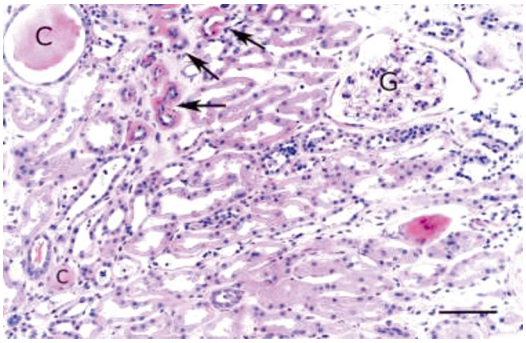


Fig. 4.4 Cadmium-associated kidney injury. Tubular atrophy and dilatation—glomerular sclerosis. (Adapted from Barregard L et al. [105])

A significant number of investigations have linked exposure to cadmium with nephrolithiasis, possibly due to increased calcium excretion as a consequence of tubular injury.

4.10 Arsenic

Arsenic is a metal found in the environment, and the highest concentrations of its inorganic form are found in soils and plants. Water contamination by arsenic, mainly in cisterns, represents a serious problem in Latin America [171].

Nephrotoxicity occurs due to the inhibition of cellular respiration by oxidative stress, with depletion of glutathione and ATP in the proximal tubule. Arsenic induces fibrogenic changes in human kidney epithelial cells through epigenetic alterations in DNA methylation. However, its association with the development of chronic kidney disease is not clear [172].

Acute arsenic poisoning can cause tubular necrosis and tubulointerstitial nephritis. Environmental, occupational, and ingestion exposure to arsenic from cistern water with high arsenic content can cause kidney damage.

The other important aspect of chronic arsenic toxicity is its effect on the cardiovascular system such as arterial hypertension [173].

From a metabolic perspective, arsenic may be related to the appearance of prediabetes, diabetes, and metabolic syndrome [174].

4.11 Lead

Nephrotoxicity is caused by the induction of oxidative stress at the mitochondrial level with an increase in reactive species and the inflammatory phenomenon due to the activation of α-2-macroglobulin (α-2 M), monocyte chemotactic attraction protein (MCP-1), and transforming growth factor beta-1 (TGFβ-1) [175, 176].

Diagnosis is made by identifying the source of exposure and blood lead levels, generally greater than 40 μg/dL. The kidney injury molecule-1 (KIM-1), α-glutathione-S-transferase (αGST), and N-acetyl-β-D-glucosaminidase appear to be appropriate markers.

From the anatomopathological point of view, vacuolization and degeneration of the proximal tubule cells with intranuclear inclusions are observed in acute poisoning. (Fig. 4.5).

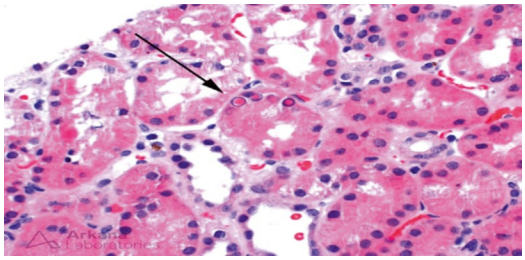


Fig. 4.5 Lead-associated acute kidney injury. Degeneration and vacuolization of proximal tubule cells, intranuclear inclusions (arrow). (Image by Dr. David Bourne (Arkana Laboratories, USA))

Long-term poisoning may induce interstitial fibrosis (chronic tubulointerstitial nephropathy with nephrosclerosis). Histopathological examination shows focal or diffuse interstitial fibrosis, with little inflammatory infiltrate, dilatation, tubular atrophy and fibrosis of the adventitia of small arteries, and subsequently glomerular fibrotic lesion (Fig. 4.6).

Lead poisoning with nephropathy secondary to projectiles lodged for a long time in the human body, especially in the intra-articular spaces, has been described. In the current era of global violence, the possible chronic lead poisoning by projectiles must be taken into account in the genesis of chronic kidney disease [177–179] (Fig. 4.7).

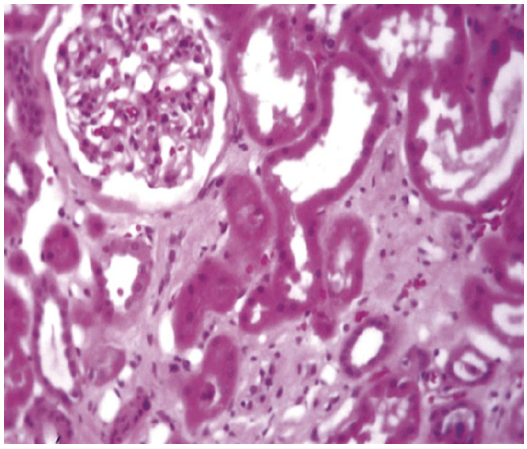


Fig. 4.6 Lead-associated chronic kidney disease. Atrophy and tubular dilatation—interstitial fibrosis. (Image by Dr. Vecihi Batuman, MD, FASN (Tulane School of Medicine, USA))

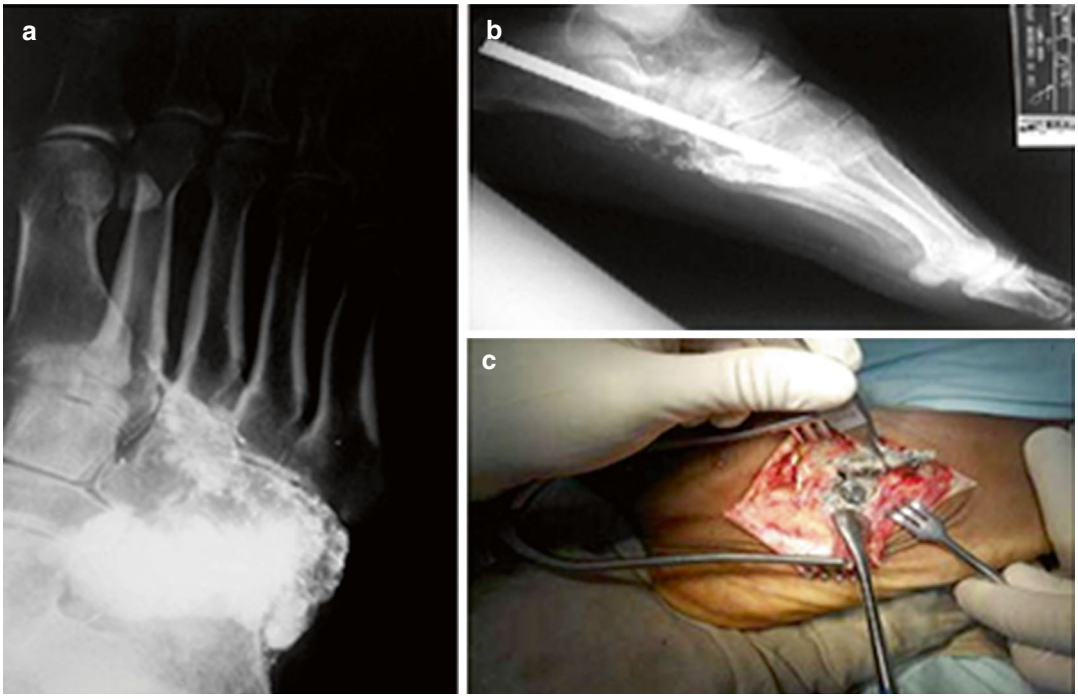


Fig. 4.7 (**a**) A 43-year-old man was admitted for recurrent quadriplegia, arterial hypertension, anemia, and chronic renal failure grade IV. (**b**) History of gunshot wound to the left foot several years earlier. (**c**) Blood lead 64 μ/dL (normal 5 μ/dL). (Images by Gerstner-Garcés JB [177]. Courtesy by Dr. Juan Bernardo Gerstner-Garcés (Clínica Imbanaco, Colombia))

4.12 Chronic Lead Poisoning and Chronic Kidney Disease

4.12.1 Projectile Lodged in the Joint of the Left Foot

Exposure to lead at high concentrations and for a long time leads to damage to the proximal tubules with Fanconi syndrome, consisting of glucosuria, aminoaciduria, and phosphaturia, which reflect a decrease in the absorption of these elements. Subsequently, there is an increase in serum creatinine and a decrease in the glomerular filtration rate, scant proteinuria, relatively normal urinary sediment, hyperuricemia, and a history of gout. Hyperfiltration can initially be observed when blood lead levels are high, as has been observed in workers who work with lead in Korea, Taiwan, Belgium, and Poland. In addition, this phenomenon has been observed in European children poisoned with lead. Lead exposure, even at low levels (<10 μg/dL), may be related to kidney damage, with a decrease in the glomerular filtration rate, with an increase in tubular injury markers and glomeruli, according to some research in population groups [180–183].

A systematic analysis of the burden of chronic kidney disease attributable to lead exposure showed an increase between 1990 and 2019 and its mortality, especially in Latin America [184].

It has been observed that exposure to low levels of lead can lead to iron deficiency in kidney patients with advanced kidney disease [112, 113].

Lead poisoning affects endothelial cells, with an increase in free radicals, oxidative stress, and the inflammatory process. The synthesis of nitric oxide decreases, and there is also an activation of

the sympathetic nervous system and an increase in the expression of angiotensinogen, plasma renin activity, angiotensin II, and aldosterone. There is an increase in endothelin, a reduction in vasodilatory prostaglandins, and activation of thromboxane generation.

One of the consequences of chronic lead poisoning may be arterial hypertension, especially in African descendants, which may be a risk factor for developing chronic kidney disease [101].

Several studies have linked environmental exposure to lead with hyperuricemia and renal lithiasis, which are important factors for developing kidney damage.

The indicated treatment is chelation with EDTA and DMSA, which could delay the progression of chronic kidney disease due to lead poisoning.

4.13 Other Nephrotoxic Metals and Metalloids

4.13.1 Silica

Occupational exposure to silica is primarily responsible for lung lesions called silicosis. Inhalation of silica dust by respiratory route is observed in mines, glass manufacturing, pottery, ceramics, and cement production.

Kidney injury consists of degenerative changes of the tubular epithelium, inflammation, and interstitial fibrosis.

Occupational exposure to silica and silicosis are associated with an increased prevalence of chronic kidney disease and may be related to the etiology of chronic kidney injury of unknown origin in some regions of the world [185, 186].

Exposure to silica has been associated with autoimmune diseases and ANCA-positive glomerulonephritis and vasculitis [187, 188].

Urinary biomarkers include albumin, low molecular weight proteins, kidney injury molecule-1 (KIM-1) in urine, and liver-like fatty acid-binding protein (L-FABP) [189, 190].

4.13.2 Chrome

Toxicity results when hexavalent chromium enters renal cells, causing severe damage with autophagy and apoptosis by activation of caspase-3 and polymerases [191].

An increase in renal damage biomarkers such as proteinuria and kidney injury molecule-1 (KIM-1) has been observed in leather tannery workers, with elevated levels of chromium in urine [192].

4.13.3 Lithium

It is used in the battery industry and in bipolar disorders. Toxicity from the ingestion of lithium compounds leads to resistance to the antidiuretic hormone essential for urine concentration, leading to nephrogenic diabetes insipidus characterized by polydipsia and polyuria, present in 20–40% of patients.

From the anatomopathological point of view, focal segmental and global glomerulosclerosis are observed, as well as interstitial fibrosis with tubular atrophy and little inflammation. Distal and colected duct microcysts [193].

Long-term administration of lithium for bipolar disorder produces chronic tubulointerstitial nephritis, manifested by a progressive decrease in the glomerular filtration rate that sets in insidiously and occasionally progresses to chronic kidney disease in 25% of patients [194–196].

4.13.4 Organic Solvents

In the kidney, they cause damage to the glomeruli, tubules, and interstitium. It is slow-developing and difficult to identify with traditional markers in its early stages.

Acute exposure causes acute kidney injury with tubular necrosis and eventually tubulointerstitial nephritis.

Chronic exposure can cause glomerulonephritis with progression to chronic kidney disease. It has been associated with Goodpasture syndrome due to the formation of antibodies against the glomerular basement membrane due to alveolar chemical damage. The association with membranous nephropathy is also described [197].

Exposure to benzene in children who work in precarious conditions showed proteinuria and increased biomarkers of kidney injury such as cystatin C (Cys-C), osteopontin (OPN), α1-microglobulin (α-MG), and neutrophil gelatinase associated with lipocalin [198].

A systematic review and meta-analysis found that exposure to a mixture of organic solvents increases the risk of chronic kidney disease [199].

4.13.5 Pesticides

There is evidence that pesticides induce oxidative stress caused by reactive oxygen and nitrogen molecules, which activate a series of mechanisms that lead to inflammation and cellular apoptosis due to mitochondrial damage [200].

Pesticide poisoning causes acute kidney injury, the resolution of which is sometimes not complete and can progress to interstitial fibrosis. Continued exposure, even at low doses, can lead to chronic kidney disease [201–203].

Glyphosate poisoning is the cause of acute kidney injury in 24–36% of patients [204–206].

The most useful biomarkers in the early diagnosis of acute kidney toxicity due to agrochemicals include kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) and β2-microglobulin (β2-MG) [207, 208].

Elevated levels of paraquat and glyphosate in Sri Lankan sugarcane farmers increased KIM-1, NGAL, and β2-MG and decreased glomerular filtration rate [209].

Malathion exposure increased the risk of decreased glomerular filtration rate in the general US population according to the NHANES database from 2001 to 2010. Malathion may also cause nephrotic syndrome [202, 210].

Chronic exposure to several common pesticides among licensed applicators of these compounds was associated with the risk of developing chronic kidney disease in a study on agriculture and health in the United States [211].

A study in Seville, Spain, in rural women indirectly exposed to pesticides, revealed subclinical renal damage identified by glomerular filtration rate, albuminuria, and early biomarkers of renal damage (KIM-1, NAG, and NGAL) [212].

A systematic review of meta-analysis of risk factors in chronic kidney disease due to non-traditional causes revealed a statistically significant association between this type of pathological entity and pesticides [213].

It is striking that in most areas where chronic kidney disease of undetermined origin is found, almost always in farmers, the application of agrochemicals is among the risk factors and these compounds are repeatedly involved in its etiology [214–216].

4.14 Herbal and Other Product-Related Nephropathy

Aristolochic acid, present in several Chinese herbs, is involved in the etiology of a type of chronic interstitial nephropathy [217].

Contamination and adulteration of herbal products, generically called "natural," are of concern. These products contain, in some cases, heavy metals, pesticides, and drugs prescribed by physicians. This problem is more worrying for diabetic, hypertensive, and chronic kidney disease patients.

In view of their widespread use, the ingestion of herbal products, mainly from Asia, should always be considered in the examination of patients with unexplained kidney disease [218, 219].

4.14.1 Aristolochic Acid

Studies in habitual users of herbal medicines containing aristolochic acid showed that they

exhibited significant albuminuria and decreased glomerular filtration rate. There is a significant risk of chronic kidney disease with the consumption of some Chinese herbal preparations, mainly those containing Mu Tong and Fangchi. In some patients with end-stage renal disease, a history of exposure to herbal remedies has been noted [220–222].

Clinically, it presents as a picture of progressive chronic kidney disease, with increased creatinine, decreased glomerular filtration rate, and anemia. Blood pressure is normal or slightly elevated. Low-grade proteinuria, sediment with few red blood cells and white blood cells, glucosuria and tubular aminoaciduria, decreased urinary concentration. Increased excretion of low weight proteins derived from tubular origin: IgM light chains, robonuclease, β2-microglobulin, uromodulin (Tamm-Horsfall protein), and RBP (retinol-binding protein). Pathologically, the main lesion is in the renal cortex, with extensive interstitial fibrosis, tubular atrophy, and little cellular infiltration [223–225].

4.15 Other Substances Associated with Nephrotoxicity and Risk Factors for Chronic Kidney Disease

Endocrine disruptors interfere with hormone synthesis, metabolism, and action, altering metabolism (diabetes mellitus, metabolic syndrome, obesity) and the cardiovascular system with endothelial dysfunction (arterial hypertension) [226].

The most common endocrine disruptors are industrial solvents and their derivatives, dioxins, plastics (bisphenol A), plasticizers (phthalates), flame retardants, pesticides, fungicides, and some metals and metalloids.

The renal accumulation of dioxins, bisphenol, and phthalates affects the glomeruli and renal tubules and can cause proteinuria and tubulointerstitial fibrosis. Chronic exposure to bisphenol A has been associated with the appearance of low-level albuminuria in the adult population, children, and adolescents [119, 227].

Bisphenol A and its substitutes bisphenol S and F cause hyperuricemia and gout according to a study in adults in the United States [228].

Exposure to bisphenol A, phthalates, and other contaminants is associated with oxidative stress, inflammation, endothelial dysfunction, and insulin resistance and is a risk factor for the development of diabetes mellitus [229, 230].

Several studies have suggested that phthalates may be associated with markers of glomerular and tubular renal injury (albumin/creatinine ratio, β2-microglobulin, NAG).

Long-term exposure to high levels of phthalates causes a decrease in the glomerular filtration rate and an increase in the albumin/creatinine ratio (UACR) [7].

Greater progression of chronic kidney disease has been observed with exposure to phthalates [231]. Polystyrene microplastics are small fragments resulting from the decomposition of the same, by physical, chemical, or biological processes, and accumulate in the tissues of the organs and in the body fluids. In the kidney, they can produce oxidative stress and inflammation and promote autophagy of the kidney cells, according to experimental studies, eventually leading to alterations in kidney function due to nephrotoxicity [232–234].

4.16 Conclusions

Environmental pollution is now considered, together with genetics, as a contributing factor for the appearance of chronic kidney disease, along with traditional risk factors such as diabetes, hypertension, obesity, and metabolic syndrome.

Environmental, occupational, and intramural toxic nephropathy has not received, until now, sufficient attention as a contributing agent in the origin of chronic kidney damage.

Toxic nephropathy, which frequently produces acute kidney injury, can be an important risk factor for the development of chronic kidney disease and its progression.

Exposure to toxic substances, both acutely and chronically, leads to kidney damage that may

go unnoticed until irreversible kidney damage has been established, generally caused by a chronic tubulointerstitial injury with subsequent involvement of the glomeruli and vessels.

Prevention of kidney disease should begin in childhood and adolescence because several studies have shown incipient kidney damage such as hematuria and proteinuria in these age groups. Studies of urinary screening in several countries have demonstrated its usefulness for the early diagnosis and prognosis of kidney disease manifested by proteinuria and hematuria in schoolchildren. In our study, 9951 schoolchildren had significant percentages of hematuria and proteinuria in at least 2 cities. Technologically, the test was repeated with the dipstick and manual urinary sediment twice to rule out false positives [1, 235–238].

Prevention should also be aimed at analyzing age groups such as children and adolescents in which renal damage may possibly begin. The study of elderly people is also very important because the prevalence of chronic kidney disease in this group is quite significant [239].

The prevention of kidney disease and its progression should be aimed, in addition to the use of traditional markers, at establishing identification of tubular lesions, by means of specific tubulointerstitial biomarkers, in order to intervene early in reversible stages, to avoid its progression to chronic renal pathological conditions.

Most kidney disease prevention programs are based on the glomerular filtration rate calculated on the basis of serum creatinine and the increase in microalbuminuria, omitting other tubular lesion markers, which are often earlier indices of renal involvement. These traditional markers are imprecise because they are chronic tubulointerstitial lesions and the calculated glomerular filtration rate is a late indicator to identify renal injury. Therefore, the application of specific indicators of nephrotoxicity is imperative.

Despite the efforts aimed at reducing the prevalence of chronic disease worldwide, through established programs, this continues to increase in most countries, particularly in Latin America, and unfortunately, they have not included toxic nephropathy as a causal coadjuvant agent.

Currently available data imply that, with early interventions on risk factors, including knowledge about nephrotoxic substances and their biomarkers of renal injury, the development of chronic kidney disease could be prevented, its progression slowed, and its complications reduced.

4.17 Take-Home Message

- Prevention of kidney disease should begin in childhood and adolescence through urinary screening and other diagnostic methods.
- High blood pressure and chronic kidney disease have a higher incidence with advancing age. Therefore, greater attention is required, given the greater susceptibility to nephrotoxins.
- In addition to traditional renal indicators, more specific renal biomarkers should be implemented for the early detection and monitoring of chronic kidney disease due to nephrotoxins.

References

1. Sanclemente E. Contaminación ambiental, ocupación y enfermedades del riñón. Cali: Feriva; 2015. 232 p.
2. Koyama H, Kamogashira T, Yamasoba T. Heavy metal exposure: molecular pathways, clinical implications, and protective strategies. Antioxidants (Basel). 2024;13(1):76.
3. Hantrakool S, Kumfu S, Chattipakorn SC, et al. Effects of particulate matter on inflammation and thrombosis: past evidence for future prevention. IJERPH. 2022;19(14):8771.
4. Ortega-Moctezuma O, Zárate-Pérez J, Alba-Alba CM, et al. Enfermedad renal crónica asociada a la exposición a metales pesados y productos agroquímicos en Latinoamérica. Enferm Nefrol. 2023;26(2):120–31.
5. Kshirsagar AV, Zeitler EM, Weaver A, et al. Environmental exposures and kidney disease. Kidney360. 2022;3(12):2174–82.
6. Park J, Yun H, Lee W. Greenness and kidney? A review of epidemiological studies on the association between green space and kidney disease. Kidney Res Clin Pract. 2024;43(1):63–70.
7. Chen CY, Lee CC, Hsu HJ, Wu IW, Chen YC, Pan HC, et al. Long-term impacts of endocrine-

disrupting chemicals exposure on kidney function: a community-based cohort study. Environ Toxicol Pharmacol. 2024;106:104379.
8. Sato Y, Roncal-Jimenez CA, Andres-Hernando A, Jensen T, Tolan DR, Sanchez-Lozada LG, et al. Increase of core temperature affected the progression of kidney injury by repeated heat stress exposure. Am J Physiol Renal Physiol. 2019;317(5):F1111–21.
9. Al-Bouwarthan M, AlMulla AA, Yaseen M. The impact of heat on kidney health: a PRISMA-compliant bibliometric analysis. Medicine. 2022;101(36):e30328.
10. Luna-Cerón E, Pherez-Farah A, Krishnan-Sivadoss I, Guerrero-Beltrán CE. Molecular challenges and opportunities in climate change-induced kidney diseases. Biomol Ther. 2024;14(3):251.
11. Wang X, Karvonen-Gutierrez CA, Herman WH, et al. Urinary heavy metals and longitudinal changes in blood pressure in midlife women: the study of women's health across the nation. Hypertension. 2021;78(2):543–51.
12. Hsu CN, Tain YL. Adverse impact of environmental chemicals on developmental origins of kidney disease and hypertension. Front Endocrinol. 2021;12:745716.
13. Jia G, Sowers JR. Hypertension in diabetes: an update of basic mechanisms and clinical disease. Hypertension. 2021;78(5):1197–205.
14. Chen H, Zou Y, Leng X, et al. Associations of blood lead, cadmium, and mercury with resistant hypertension among adults in NHANES, 1999–2018. Environ Health Prev Med. 2023;28(0):66.
15. Penno G, Solini A, Bonora E, et al. Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. J Hypertens. 2011;29(9):1802–9.
16. Mottl AK, Kwon KS, Mauer M, et al. Normoalbuminuric diabetic kidney disease in the U.S. Popul J Diabetes Complic. 2013;27(2):123–7.
17. Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep. 2020;10(1):14790.
18. Tuttle KR, Agarwal R, Alpers CE, Bakris GL, Brosius FC, Kolkhof P, et al. Molecular mechanisms and therapeutic targets for diabetic kidney disease. Kidney Int. 2022;102(2):248–60.
19. De Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and kidney disease: improving global outcomes (KDIGO). Diabetes Care. 2022;45(12):3075–90.
20. Schrauben SJ, Shou H, Zhang X, et al. Association of Multiple Plasma Biomarker Concentrations with progression of prevalent diabetic kidney disease: findings from the chronic renal insufficiency cohort (CRIC) study. JASN. 2021;32(1):115–26.
21. Chan TYK, Chan APL, Tang HL. Nephrotic syndrome caused by exposures to skin-lightening cosmetic products containing inorganic mercury. Clin Toxicol. 2020;58(1):9–15.
22. Chang J, Yan J, Li X, Liu N, Zheng R, Zhong Y. Update on the mechanisms of tubular cell injury in diabetic kidney disease. Front Med. 2021;8:661076.
23. Cai F, Zhang L, Han F. POS-187 prognostic roles of tubular injury markers in diabetic nephropathy. Kidney Int Rep. 2022;7(2):S81.
24. Wang X, Li A, Xu Q. The association between urinary polycyclic aromatic hydrocarbons metabolites and type 2 diabetes mellitus. IJERPH. 2022;19(13):7605.
25. Yan Z, Wang G, Shi X. Advances in the progression and prognosis biomarkers of chronic kidney disease. Front Pharmacol. 2021;12:785375.
26. Burkart K, Causey K, Cohen AJ, et al. Estimates, trends, and drivers of the global burden of type 2 diabetes attributable to PM2·5 air pollution, 1990–2019: an analysis of data from the global burden of disease study 2019. Lancet Planet Health. 2022;6(7):e586–600.
27. Letellier N, Zamora S, Spoon C, et al. Air pollution and metabolic disorders: dynamic versus static measures of exposure among Hispanics/Latinos and non-Hispanics. Environ Res. 2022;209:112846.
28. Roth K, Petriello MC. Exposure to per- and polyfluoroalkyl substances (PFAS) and type 2 diabetes risk. Front Endocrinol. 2022;13:965384.
29. Chen M, Qin Q, Liu F, et al. How long-term air pollution and its metal constituents affect type 2 diabetes mellitus prevalence? Results from Wuhan chronic disease cohort. Environ Res. 2022;212:113158.
30. Zhang Y, Gong X, Li R, et al. Exposure to cadmium and lead is associated with diabetic kidney disease in diabetic patients. Environ Health. 2024;23(1):1.
31. Wen Y, Xu L, Melchinger I, et al. Longitudinal biomarkers and kidney disease progression after acute kidney injury. JCI Insight. 2023;8(9):e167731.
32. Ortiz-Soriano V, Singh G, Chang A, et al. Processes of care in survivors of acute kidney injury followed in specialized postdischarge clinics. CJASN. 2022;17(11):1669–72.
33. Guzzi F, Cirillo L, Roperto RM, et al. Molecular mechanisms of the acute kidney injury to chronic kidney disease transition: an updated view. IJMS. 2019;20(19):4941.
34. Yu SMW, Bonventre JV. Acute kidney injury and maladaptive tubular repair leading to renal fibrosis. Curr Opin Nephrol Hypertens. 2020;29(3):310–8.
35. Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2020;395(10225):709–33.
36. Ke C, Liang J, Liu M, et al. Burden of chronic kidney disease and its risk-attributable burden in 137 low-and middle-income countries, 1990–2019: results from the global burden of disease study 2019. BMC Nephrol. 2022;23(1):17.
37. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl. 2022;12(1):7–11.

38. United States Renal Data System. 2023 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda: National Institutes of Health; 2023.
39. Floris M, Lepori N, Angioi A, et al. Chronic kidney disease of undetermined etiology around the world. Kidney Blood Press Res. 2021;46(2):142–51.
40. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. Am J Kidney Dis. 2022;79(2):268–288.e1.
41. Speeckaert MM, Seegmiller J, Glorieux G, et al. Measured glomerular filtration rate: the query for a workable Golden standard technique. JPM. 2021;11(10):949.
42. Huisman BJMV, Agyemang C, Van Den Born BJH, et al. Discrepancies in estimated glomerular filtration rate and albuminuria levels in ethnic minority groups – the multiethnic HELIUS cohort study. eClinicalMedicine. 2022;45:101324.
43. Yan AF, Williams MY, Shi Z, et al. Bias and accuracy of glomerular filtration rate estimating equations in the US: a systematic review and meta-analysis. JAMA Netw Open. 2024;7(3):e241127.
44. Zsom L, Zsom M, Salim SA, Fülöp T. Estimated glomerular filtration rate in chronic kidney disease: a critical review of estimate-based predictions of individual outcomes in kidney disease. Toxins. 2022;14(2):127.
45. Chagnac A, Friedman AN. Measuring albuminuria in individuals with obesity: pitfalls of the urinary albumin-creatinine ratio. Kidney Med. 2024;6(4):100804.
46. Tsai HJ, Hung CH, Wang CW, et al. Associations among heavy metals and proteinuria and chronic kidney disease. Diagnostics. 2021;11(2):282.
47. Greenberg JH, Abraham AG, Xu Y, et al. Plasma biomarkers of tubular injury and inflammation are associated with CKD progression in children. JASN. 2020;31(5):1067–77.
48. Taylor KM, Au AYM, Herath S, et al. Kidney functional reserve and damage biomarkers in subclinical chronic kidney disease and acute kidney injury. Am J Physiol Renal Physiol. 2023;325(6):F888–98.
49. Tin A, Köttgen A. Genome-wide association studies of CKD and related traits. CJASN. 2020;15(11):1643–56.
50. Bleyer AJ, Westemeyer M, Xie J, et al. Genetic etiologies for chronic kidney disease revealed through next-generation renal gene panel. Am J Nephrol. 2022;53(4):297–306.
51. Kim NH, Hyun YY, Lee KB, et al. Environmental heavy metal exposure and chronic kidney disease in the general population. J Korean Med Sci. 2015;30(3):272.
52. Satarug S, Gobe GC, Vesey DA, Phelps KR. Cadmium and Lead exposure, nephrotoxicity, and mortality. Toxics. 2020;8(4):86.
53. Lee J, Oh S, Kang H, et al. Environment-wide association study of CKD. CJASN. 2020;15(6):766–75.
54. Holliday MW, Li Q, Bustamante EG, et al. Potential mechanisms involved in chronic kidney disease of unclear etiology. CJASN. 2022;17(9):1293–304.
55. Gifford FJ, Gifford RM, Eddleston M, Dhaun N. Endemic nephropathy around the world. Kidney Int Rep. 2017;2(2):282–92.
56. Ghosh R, Siddarth M, Singh N, et al. Organochlorine pesticide level in patients with chronic kidney disease of unknown etiology and its association with renal function. Environ Health Prev Med. 2017;22(1):49.
57. Friedman DJ. Genes and environment in chronic kidney disease hotspots. Curr Opin Nephrol Hypertens. 2019;28(1):87–96.
58. Gothwaal C, Kalra OP, Agarwal S, Raizada A. Organochlorine pesticides: the culprit behind chronic kidney disease of unknown origin. JECE. 2020;12(2):80–6.
59. Vervaet BA, Nast CC, Jayasumana C, Schreurs G, Roels F, Herath C, et al. Chronic interstitial nephritis in agricultural communities is a toxin-induced proximal tubular nephropathy. Kidney Int. 2020;97(2):350–69.
60. Redmon JH, Levine KE, Lebov J, et al. A comparative review: chronic kidney disease of unknown etiology (CKDu) research conducted in Latin America versus Asia. Environ Res. 2021;192:110270.
61. Valdivia Mazeyra MF, Muñoz Ramos P, Serrano R, Alonso Riaño M, Gil Giraldo Y, Quiroga B. Mesoamerican nephropathy: a not so unknown chronic kidney disease. Nefrología (English Edition). 2021;41(6):612–9.
62. Cabrera Jara WE, Barreto Romero SR, Gamarra MG, et al. A new challenge for doctors in Paraguay: chronic interstitial nephritis in agricultural communities (CINAC). Rev Virtual Soc Parag Med Int. 2022;9(2):120–30.
63. Gunawickrama SHNP, Silva ARN, Nanayakkara PGCL, et al. Metals and Metallothionein expression in relation to progression of chronic kidney disease of unknown etiology (CKDu) in Sri Lanka. Diseases. 2022;10(2):34.
64. Keogh SA, Leibler JH, Sennett Decker CM, et al. High prevalence of chronic kidney disease of unknown etiology among workers in the Mesoamerican nephropathy occupational study. BMC Nephrol. 2022;23(1):238.
65. Fujimaru T, Mori T, Chiga M, et al. Genetic diagnosis of adult hemodialysis patients with unknown etiology. Kidney Int Rep. 2024;9(4):994–1004.
66. Claudel SE, Waikar SS, Amador JJ, et al. Systematic review of kidney injury biomarkers for the evaluation of CKD of uncertain etiology. Kidney Int Rep. 2024;9(6):1614–32.
67. Moeller MJ, Kramann R, Lammers T, et al. New aspects of kidney fibrosis–from mechanisms of injury to modulation of disease. Front Med. 2022;8:814497.

68. Liu X, Li X, Chen Y, et al. Systemic immune-inflammation index is associated with chronic kidney disease in the U.S. population: insights from NHANES 2007–2018. Front Immunol. 2024;15:1331610.
69. AIRG-E, EKPF, ALCER, et al. CKD: the burden of disease invisible to research funders. Nefrologia. 2022;42(1):65–84.
70. Kalantari K. Assessing tubular function, an ignored component of CKD, might be a difference maker! JASN. 2022;33(10):1806–8.
71. Mizdrak M, Kumrić M, Kurir TT, Božić J. Emerging biomarkers for early detection of chronic kidney disease. JPM. 2022;12(4):548.
72. Petreski T, Piko N, Ekart R, et al. Review on inflammation markers in chronic kidney disease. Biomedicines. 2021;9(2):182.
73. Yan LJ, Allen DC. Cadmium-induced kidney injury: oxidative damage as a unifying mechanism. Biomol Ther. 2021;11(11):1575.
74. Amatruda JG, Katz R, Sarnak MJ, et al. Biomarkers of kidney tubule disease and risk of end-stage kidney disease in persons with diabetes and CKD. Kidney Int Rep. 2022;7(7):1514–23.
75. Bowe B, Xie Y, Li T, et al. Estimates of the 2016 global burden of kidney disease attributable to ambient fine particulate matter air pollution. BMJ Open. 2019;9(5):e022450.
76. Briffa J, Sinagra E, Blundell R. Heavy metal pollution in the environment and their toxicological effects on humans. Heliyon. 2020;6(9):e04691.
77. Al-Aly Z, Bowe B. Air pollution and kidney disease. CJASN. 2020;15(3):301–3.
78. Li G, Huang J, Wang J, et al. Long-term exposure to ambient PM2.5 and increased risk of CKD prevalence in China. JASN. 2021;32(2):448–58.
79. Afsar B, Elsurer Afsar R, Kanbay A, et al. Air pollution and kidney disease: review of current evidence. Clin Kidney J. 2019;12(1):19–32.
80. Wang C, Tsai JD, Wan L, et al. Association between gaseous air pollutants and idiopathic nephrotic syndrome in children: a 12-year population-based cohort study. Ital J Pediatr. 2022;48(1):70.
81. Guo C, Chang LY, Wei X, et al. Multi-pollutant air pollution and renal health in Asian children and adolescents: an 18-year longitudinal study. Environ Res. 2022;214:114144.
82. Xu X, Wang G, Chen N, et al. Long-term exposure to air pollution and increased risk of membranous nephropathy in China. JASN. 2016;27(12):3739–46.
83. Politis MD, Gutiérrez-Avila I, Just A, et al. Recent ambient temperature and fine particulate matter (PM2.5) exposure is associated with urinary kidney injury biomarkers in children. Sci Total Environ. 2024;907:168119.
84. Bragg-Gresham J, Morgenstern H, McClellan W, et al. County-level air quality and the prevalence of diagnosed chronic kidney disease in the US Medicare population. De Borst MH, editor. PLoS One. 2018;13(7):e0200612.
85. Bowe B, Xie Y, Li T, et al. Particulate matter air pollution and the risk of incident CKD and progression to ESRD. JASN. 2018;29(1):218–30.
86. Blum MF, Surapaneni A, Stewart JD, et al. Particulate matter and albuminuria, glomerular filtration rate, and incident CKD. CJASN. 2020;15(3):311–9.
87. Tsai HJ, Wu PY, Huang JC, Chen SC. Environmental pollution and chronic kidney disease. Int J Med Sci. 2021;18(5):1121–9.
88. Liu H, Shao X, Jiang X, et al. Joint exposure to outdoor ambient air pollutants and incident chronic kidney disease: a prospective cohort study with 90,032 older adults. Front Public Health. 2022;10:992353.
89. Wu YH, Wu CD, Chung MC, et al. Long-term exposure to fine particulate matter and the deterioration of estimated glomerular filtration rate: A cohort study in patients with pre-end-stage renal disease. Front Public Health. 2022;10:858655.
90. Li S, Meng Q, Laba C, et al. Associations between long-term exposure to ambient air pollution and renal function in Southwest China: the China multiethnic cohort (CMEC) study. Ecotoxicol Environ Saf. 2022;242:113851.
91. Dai Y, Yin J, Li S, et al. Long-term exposure to fine particulate matter constituents in relation to chronic kidney disease: evidence from a large population-based study in China. Environ Geochem Health. 2024;46(5):174.
92. Wathanavasin W, Banjongjit A, Phannajit J, et al. Association of fine particulate matter (PM2.5) exposure and chronic kidney disease outcomes: a systematic review and meta-analysis. Sci Rep. 2024;14(1):1048.
93. Wu MY, Lo WC, Chao CT, et al. Association between air pollutants and development of chronic kidney disease: a systematic review and meta-analysis. Sci Total Environ. 2020;706:135522.
94. Xu W, Jia L, Lin Y, et al. Association of air pollution and risk of chronic kidney disease: a systematic review and meta-analysis. J Biochem Molecular Tox. 2024;38(1):e23610.
95. Yang C, Wang W, Wang F, et al. Ambient PM2.5 components and prevalence of chronic kidney disease: a nationwide cross-sectional survey in China. Environ Geochem Health. 2024;46(2):70.
96. Wang Y, Zhang H, Tang P, et al. Association between blood metals mixture and chronic kidney disease in adults: NHANES 2013–2016. J Trace Elem Med Biol. 2024;83:127395.
97. Kim E, Huh H, Mo Y, et al. Long-term ozone exposure and mortality in patients with chronic kidney disease: a large cohort study. BMC Nephrol. 2024;25(1):74.
98. Peng S, Chen B, Li Z, et al. Ambient ozone pollution impairs glucose homeostasis and contributes to renal function decline: population-based evidence. Ecotoxicol Environ Saf. 2024;269:115803.
99. Parasin N, Amnuaylojaroen T, Saokaew S. Effect of air pollution on obesity in children: a systematic review and meta-analysis. Children. 2021;8(5):327.

100. Basith S, Manavalan B, Shin TH, et al. The impact of fine particulate matter 2.5 on the cardiovascular system: a review of the invisible killer. Nano. 2022;12(15):2656.
101. Huang Z. Association between blood Lead level with high blood pressure in US (NHANES 1999–2018). Front Public Health. 2022;10:836357.
102. Shang Z, Gao YM, Deng ZL, Wang Y. Long-term exposure to ambient air pollutants and increased risk of end-stage renal disease in patients with type 2 diabetes mellitus and chronic kidney disease: a retrospective cohort study in Beijing, China. Environ Sci Pollut Res. 2023;31(4):5429–43.
103. Balali-Mood M, Naseri K, Tahergorabi Z, et al. Toxic mechanisms of five heavy metals: mercury, lead, chromium, cadmium, and arsenic. Front Pharmacol. 2021;12:643972.
104. Zhao L, Chen X, Chen Z, et al. Association of metal exposure with novel immunoinflammatory indicators. Toxics. 2024;12(5):316.
105. Barregard L, Sallsten G, Lundh T, Mölne J. Low-level exposure to lead, cadmium and mercury, and histopathological findings in kidney biopsies. Environ Res. 2022;211:113119.
106. Rawee P, Kremer D, Nolte IM, et al. Iron deficiency and nephrotoxic heavy metals: a dangerous interplay? IJMS. 2023;24(6):5315.
107. Jalili C, Kazemi M, Cheng H, et al. Associations between exposure to heavy metals and the risk of chronic kidney disease: a systematic review and meta-analysis. Crit Rev Toxicol. 2021;51(2):165–82.
108. Park Y, Lee SJ. Association of blood heavy metal levels and renal function in Korean adults. IJERPH. 2022;19(11):6646.
109. Haruna I, Obeng-Gyasi E. Association of combined per- and Polyfluoroalkyl substances and metals with chronic kidney disease. IJERPH. 2024;21(4):468.
110. Nan Y, Yang J, Yang J, et al. Associations between individual and combined metal exposures in whole blood and kidney function in U.S. adults aged 40 years and older. Biol Trace Elem Res. 2024;202(3):850–65.
111. Akinleye A, Oremade O, Xu X. Exposure to low levels of heavy metals and chronic kidney disease in the US population: a cross sectional study. Al-Saleh I, editor. PLoS One. 2024;19(4):e0288190.
112. Danziger J, Dodge LE, Hu H, Mukamal KJ. Susceptibility to environmental heavy metal toxicity among Americans with kidney disease. Kidney360. 2022;3(7):1191–6.
113. Danziger J, Mukamal KJ. Levels of Lead in residential drinking water and iron deficiency among patients with end stage kidney disease. Kidney360. 2022;3(7):1210–6.
114. Qing Y, Zheng J, Tang T, et al. Risk assessment of combined exposure to lead, cadmium, and total mercury among the elderly in Shanghai, China. Ecotoxicol Environ Saf. 2023;256:114874.
115. Sung JM, Chang WH, Liu KH, et al. The effect of co-exposure to glyphosate, cadmium, and arsenic on chronic kidney disease. Expo Health. 2022;14(3):779–89.
116. Tan Y, Fu Y, Huang F, Wen L, Weng X, Yao H, et al. Association between blood metal exposures and hyperuricemia in the U.S. general adult: a subgroup analysis from NHANES. Chemosphere. 2023;318:137873.
117. Lu LH, Tsai CC, Lin CY, et al. Association and interaction between heavy metals and hyperuricemia in a Taiwanese population. Diagnostics. 2023;13(10):1741.
118. Pollard KM, Cauvi DM, Mayeux JM, et al. Mechanisms of environment-induced autoimmunity. Annu Rev Pharmacol Toxicol. 2021;61(1):135–57.
119. Zhang X, Flaws JA, Spinella MJ, Irudayaraj J. The relationship between typical environmental endocrine disruptors and kidney disease. Toxics. 2022;11(1):32.
120. Yimthiang S, Pouyfung P, Khamphaya T, et al. Effects of environmental exposure to cadmium and Lead on the risks of diabetes and kidney dysfunction. IJERPH. 2022;19(4):2259.
121. Yang J, Chan K, Choi C, et al. Identifying effects of urinary metals on type 2 diabetes in U.S. adults: cross-sectional analysis of national health and nutrition examination survey 2011–2016. Nutrients. 2022;14(8):1552.
122. Lin CJ, Shih HM, Wu PC, et al. Plasma selenium and zinc alter associations between nephrotoxic metals and chronic kidney disease: results from NHANES database 2011–2018. Ann Acad Med Singap. 2023;52(8):398–410.
123. Pócsi I, Dockrell ME, Price RG. Nephrotoxic biomarkers with specific indications for metallic pollutants: implications for environmental health. Biomark Insights. 2022;17:117727192211118.
124. Ekanayake EMDV, Gunasekara TDKSC, De Silva PMCS, et al. Applicability of novel urinary biomarkers for the assessment of renal injury in selected occupational groups in Sri Lanka: a comparative study with conventional markers. IJERPH. 2022;19(9):5264.
125. Catanese L, Rupprecht H, Huber TB, et al. Non-invasive biomarkers for diagnosis, risk prediction, and therapy guidance of glomerular kidney diseases: a comprehensive review. IJMS. 2024;25(6):3519.
126. Wu YS, Osman AI, Hosny M, et al. The toxicity of mercury and its chemical compounds: molecular mechanisms and environmental and human health implications: a comprehensive review. ACS Omega. 2024;9(5):5100–26.
127. Meneses HDNDM, Oliveira-da-Costa M, Basta PC, et al. Mercury contamination: a growing threat to riverine and urban communities in the Brazilian Amazon. IJERPH. 2022;19(5):2816.
128. Zhao M, Li Y, Wang Z. Mercury and mercury-containing preparations: history of use, clinical applications, pharmacology, toxicology, and pharmacokinetics in traditional Chinese medicine. Front Pharmacol. 2022;13:807807.

129. Sathe K, Ali U, Ohri A. Acute renal failure secondary to ingestion of ayurvedic medicine containing mercury. Indian J Nephrol. 2013;23(4):301.
130. Crespo-Lopez ME, Arrifano GP, Augusto-Oliveira M, et al. Mercury in the Amazon: the danger of a single story. Ecotoxicol Environ Saf. 256:114895.
131. Branco V, Caito S, Farina M, et al. Biomarkers of mercury toxicity: past, present, and future trends. J Toxic Environ Health, Part B. 2017;20(3):119–54.
132. Tang HL, Mak YF, Chu KH, et al. Minimal change disease caused by exposure to mercury-containing skin lightening cream: a report of 4 cases. Clin Nephrol. 2013;79:326–34.
133. Doshi M, Annigeri RA, Kowdle PC, et al. Membranous nephropathy due to chronic mercury poisoning from traditional Indian medicines: report of five cases. Clin Kidney J. 2019;12(2):239–44.
134. Qin AB, Su T, Wang SX, Zhang F, Zhou F, Zhao MH. Mercury-associated glomerulonephritis: a retrospective study of 35 cases in a single Chinese center. BMC Nephrol. 2019;20(1):228.
135. Chang J, Yan J, Li X, et al. Update on the mechanisms of tubular cell injury in diabetic kidney disease. Front Med. 2021;8:661076.
136. Qin AB, Lin ZS, Wang SX, Wang H, Cui Z, Zhou F, et al. Comparison of ultrastructural features between patients with mercury-associated membranous nephropathy and idiopathic membranous nephropathy. Am J Med Sci. 2021;361(3):327–35.
137. Gao Z, Wu N, Du X, et al. Toxic nephropathy secondary to chronic mercury poisoning: clinical characteristics and outcomes. Kidney Int Rep. 2022;7(6):1189–97.
138. Veronika E, Hartono B, Rahman A. Glomerulus filtration rate (GFR) estimation value using Cockcroft and gault equation against community exposure to mercury at artisanal and small scale gold mining (ASGM) area in Lebaksitu Village, District of Lebak, Banten. KLS. 2019;4(10):269.
139. Hardiyanti F, Hermawati E, Fitria L, et al. The association between levels of mercury in the hair with proteinuria on scavengers in Cipayung Landfill Area, Depok City, West Java, Indonesia. Indian J Public Health Res Dev. 2020;11(4):1726.
140. Rodríguez LHS, Rodríguez-Villamizar LA, Flórez-Vargas O, Fiallo YV, Ordoñez Á, Gutiérrez MDC. No effect of mercury exposure on kidney function during ongoing artisanal gold mining activities in Colombia: a cross-sectional study. Toxicol Ind Health. 2017;33(1):67–78.
141. Rodriguez-Villamizar LA, Medina OM, Flórez-Vargas O, et al. Chemical element mixtures and kidney function in mining and non-mining settings in northern Colombia. IJERPH. 2023;20(3):2321.
142. Bridges CC, Zalups RK. The aging kidney and the nephrotoxic effects of mercury. J Toxic Environ Health, Part B. 2017;20(2):55–80.
143. Hu XF, Singh K, Chan HM. Mercury exposure, blood pressure, and hypertension: a systematic review and dose–response meta-analysis. Environ Health Perspect. 2018;126(7):076002.
144. Crowe W, Allsopp PJ, Watson GE, et al. Mercury as an environmental stimulus in the development of autoimmunity – a systematic review. Autoimmun Rev. 2017;16(1):72–80.
145. Price RG. Cadmium nephropathy and smoking. Clin Med Insights Urol. 2017;10:117956111772609.
146. Eid HA, Moazen EM, Elhussini M, et al. The influence of smoking on renal functions among apparently healthy smokers. JMDH. 2022;15:2969–78.
147. Fu YC, Xu ZL, Zhao MY, Xu K. The association between smoking and renal function in people over 20 years old. Front Med. 2022;9:870278.
148. Lang SM, Schiffl H. Smoking status, cadmium, and chronic kidney disease. Ren Replace Ther. 2024;10(1):17.
149. Nordberg M, Nordberg GF. Metallothionein and cadmium toxicology: historical review and commentary. Biomol Ther. 2022;12(3):360.
150. Rana MN, Tangpong J, Rahman M. Toxicodynamics of lead, cadmium, mercury and arsenic- induced kidney toxicity and treatment strategy: a mini review. Toxicol Rep. 2018;5:704–13.
151. Liu Q, Zhang R, Wang X, et al. Effects of subchronic, low-dose cadmium exposure on kidney damage and potential mechanisms. Ann Transl Med. 2019;7(8):177.
152. Hossein-Khannazer N, Azizi G, Eslami S, et al. The effects of cadmium exposure in the induction of inflammation. Immunopharmacol Immunotoxicol. 2020;42(1):1–8.
153. Wang D, Sun H, Wu Y, et al. Tubular and glomerular kidney effects in the Chinese general population with low environmental cadmium exposure. Chemosphere. 2016;147:3–8.
154. Eom SY, Seo MN, Lee YS, et al. Low-level environmental cadmium exposure induces kidney tubule damage in the general population of Korean adults. Arch Environ Contam Toxicol. 2017;73(3):401–9.
155. Satarug S, Boonprasert K, Gobe GC, et al. Chronic exposure to cadmium is associated with a marked reduction in glomerular filtration rate. Clin Kidney J. 2019;12(4):468–75.
156. Byber K, Lison D, Verougstraete V, et al. Cadmium or cadmium compounds and chronic kidney disease in workers and the general population: a systematic review. Crit Rev Toxicol. 2016;46(3):191–240.
157. Kumar MN, Priyamvada PS, Chellappan A, et al. Membranous nephropathy associated with indigenous Indian medications containing heavy metals. Kidney Int Rep. 2020;5(9):1510–4.
158. Smereczański NM, Brzóska MM. Current levels of environmental exposure to cadmium in industrialized countries as a risk factor for kidney damage in the general population: a comprehensive review of available data. IJMS. 2023;24(9):8413.
159. Shi Z, Taylor AW, Riley M, Byles J, Liu J, Noakes M. Association between dietary patterns, cadmium

intake and chronic kidney disease among adults. Clin Nutr. 2018;37(1):276–84.
160. Zang Y, Devleesschauwer B, Bolger PM, et al. Global burden of late-stage chronic kidney disease resulting from dietary exposure to cadmium, 2015. Environ Res. 2019;169:72–8.
161. Satarug S, Vesey DA, Gobe GC, Phelps KR. The pathogenesis of albuminuria in cadmium nephropathy. Curr Res Toxicol. 2024;6:100140.
162. Butler-Dawson J, James KA, Krisher L, et al. Environmental metal exposures and kidney function of Guatemalan sugarcane workers. J Expo Sci Environ Epidemiol. 2022;32(3):461–71.
163. Madrim MF, Ja'afar MH, Hod R. Prevalence of abnormal urinary cadmium and risk of albuminuria as a primary bioindicator for kidney problems among a healthy population. PeerJ. 2021;9:e12014.
164. Li Y, Wang H, Yu J, et al. An assessment of sensitivity biomarkers for urinary cadmium burden. BMC Nephrol. 2020;21(1):385.
165. Feng X, Zhou R, Jiang Q, et al. Analysis of cadmium accumulation in community adults and its correlation with low-grade albuminuria. Sci Total Environ. 2022;834:155210.
166. Satarug S, Gobe GC, Vesey DA. Multiple targets of toxicity in environmental exposure to low-dose cadmium. Toxics. 2022;10(8):472.
167. Li Y, Zhang Y, Wang W, Wu Y. Association of urinary cadmium with risk of diabetes: a meta-analysis. Environ Sci Pollut Res. 2017;24(11):10083–90.
168. Franceschini N, Fry RC, Balakrishnan P, et al. Cadmium body burden and increased blood pressure in middle-aged American Indians: the strong heart study. J Hum Hypertens. 2017;31(3):225–30.
169. Martins AC, Almeida Lopes ACB, Urbano MR, et al. An updated systematic review on the association between Cd exposure, blood pressure and hypertension. Ecotoxicol Environ Saf. 2021;208:111636.
170. Oosterwijk MM, Hagedoorn IJM, Maatman RGHJ, et al. Cadmium, active smoking and renal function deterioration in patients with type 2 diabetes. Nephrol Dial Transplant. 2023;38(4):876–83.
171. Bundschuh J, Armienta MA, Morales-Simfors N, et al. Arsenic in Latin America: new findings on source, mobilization and mobility in human environments in 20 countries based on decadal research 2010–2020. Crit Rev Environ Sci Technol. 2021;51(16):1727–865.
172. Chang Y, Singh KP. Arsenic induces fibrogenic changes in human kidney epithelial cells potentially through epigenetic alterations in DNA methylation. J Cell Physiol. 2019;234(4):4713–25.
173. Kaufman JA, Mattison C, Fretts AM, et al. Arsenic, blood pressure, and hypertension in the strong heart family study. Environ Res. 2021;195:110864.
174. Pánico P, Velasco M, Salazar AM, et al. Is arsenic exposure a risk factor for metabolic syndrome? A review of the potential mechanisms. Front Endocrinol. 2022;13:878280.
175. Dobrakowski M, Pawlas N, Kasperczyk A, et al. Oxidative DNA damage and oxidative stress in lead-exposed workers. Hum Exp Toxicol. 2017;36(7):744–54.
176. Metryka E, Kupnicka P, Kapczuk P, et al. Lead (Pb) as a factor initiating and potentiating inflammation in human THP-1 macrophages. IJMS. 2020;21(6):2254.
177. Gerstner Garcés JB. Intoxicación por plomo secundaria a proyectiles alojados en el cuerpo humano. Colomb Med. 2012;43(3):230–4.
178. Apte A, Bradford K, Dente C, Smith RN. Lead toxicity from retained bullet fragments: a systematic review and meta-analysis. J Trauma Acute Care Surg. 2019;87(3):707–16.
179. Kershner EK, Tobarran N, Chambers A, et al. Retained bullets and lead toxicity: a systematic review. Clin Toxicol. 2022;60(10):1176–86.
180. Reilly R, Spalding S, Walsh B, et al. Chronic environmental and occupational lead exposure and kidney function among African Americans: Dallas Lead project II. IJERPH. 2018;15(12):2875.
181. Harari F, Sallsten G, Christensson A, et al. Blood lead levels and decreased kidney function in a population-based cohort. Am J Kidney Dis. 2018;72(3):381–9.
182. Steenland K, Barry V. Chronic renal disease among lead-exposed workers. Occup Environ Med. 2020;77(6):415–7.
183. Kuraeiad S, Kotepui M. Blood Lead level and renal impairment among adults: a meta-analysis. IJERPH. 2021;18(8):4174.
184. Song J, Pan T, Xu Z, et al. A systematic analysis of chronic kidney disease burden attributable to lead exposure based on the global burden of disease study 2019. Sci Total Environ. 2024;908:168189.
185. Vupputuri S, Parks CG, Nylander-French LA, et al. Occupational silica exposure and chronic kidney disease. Ren Fail. 2012;34(1):40–6.
186. Millerick-May ML, Schrauben S, Reilly MJ, Rosenman KD. Silicosis and chronic renal disease. Am J Industrial Med. 2015;58(7):730–6.
187. Gómez-Puerta JA, Gedmintas L, Costenbader KH. The association between silica exposure and development of ANCA-associated vasculitis: systematic review and meta-analysis. Autoimmun Rev. 2013;12(12):1129–35.
188. Fukushima K, Uchida HA, Fuchimoto Y, et al. Silica-associated systemic lupus erythematosus with lupus nephritis and lupus pneumonitis: a case report and a systematic review of the literature. Medicine. 2022;101(7):e28872.
189. Mourad BH, Ashour YA. Demonstration of subclinical early nephrotoxicity induced by occupational exposure to silica among workers in pottery industry. Int J Occup Environ Med. 2020;11(2):85–94.
190. Ramadan MA, Abdelgwad M, Fouad MM. Predictive value of novel biomarkers for chronic kidney disease among workers occupationally exposed to silica. Toxicol Ind Health. 2021;37(4):173–81.

191. Zheng X, Li S, Li J, et al. Hexavalent chromium induces renal apoptosis and autophagy via disordering the balance of mitochondrial dynamics in rats. Ecotoxicol Environ Saf. 2020;204:111061.
192. Tsuchiyama T, Tazaki A, Al Hossain MA, et al. Increased levels of renal damage biomarkers caused by excess exposure to trivalent chromium in workers in tanneries. Environ Res. 2020;188:109770.
193. Fogo AB, Lusco MA, Andeen NK, Najafian B, Alpers CE. AJKD atlas of renal pathology: lithium nephrotoxicity. Am J Kidney Dis. 2017;69(1):e1–2.
194. Fransson F, Werneke U, Harju V, et al. Kidney function in patients with bipolar disorder with and without lithium treatment compared with the general population in northern Sweden: results from the LiSIE and MONICA cohorts. Lancet Psychiatry. 2022;9(10):804–14.
195. Schoretsanitis G, De Filippis R, Brady BM, et al. Prevalence of impaired kidney function in patients with long-term lithium treatment: a systematic review and meta-analysis. Bipolar Disord. 2022;24(3):264–74.
196. Pahwa M, Joseph B, Nunez NA, et al. Long-term lithium therapy and risk of chronic kidney disease in bipolar disorder: a historical cohort study. Bipolar Disord. 2021;23(7):715–23.
197. Cremoni M, Agbekodo S, Teisseyre M, et al. Toxic occupational exposures and membranous nephropathy. CJASN. 2022;17(11):1609–19.
198. Pérez-Herrera N, Díaz de León-Martínez L, Flores-Ramírez R, et al. Evaluation of benzene exposure and early biomarkers of kidney damage in children exposed to solvents due to precarious work in Ticul, Yucatán, México. Ann Glob Health. 2019;85(1):94.
199. Lim C, Oh H. Organic solvent exposure for the chronic kidney disease: updated systematic review with meta-analysis. Ann Occup Environ Med. 2023;35(1):e11.
200. Sule RO, Condon L, Gomes AV. A common feature of pesticides: oxidative stress: the role of oxidative stress in pesticide-induced toxicity. Zhou X, editor. Oxidative Med Cell Longev. 2022;2022:1–31.
201. Kimura T, Yokoyama T, Tanemoto M. Renal tubular injury by glyphosate-based herbicide. Clin Exp Nephrol. 2020;24(12):1186.
202. Wan ET, Darssan D, Karatela S, et al. Association of pesticides and kidney function among adults in the US population 2001–2010. IJERPH. 2021;18(19):10249.
203. Jacobson MH, Wu Y, Liu M, et al. Organophosphate pesticides and progression of chronic kidney disease among children: a prospective cohort study. Environ Int. 2021;155:106597.
204. Park HH, Choi KI, Lee JW, et al. Clinical characteristics and risk factors of acute kidney injury in patients with glyphosate poisoning. JKSCT. 2020;18(2):110–5.
205. Sun IO, Cho AY. Comparison of clinical characteristics of AKI in patients with glyphosate and Glufosinate herbicide poisoning: PO0094. J Am Soc Nephrol. 2020;31(10S):88.
206. Cho AY, Oh JH, Oh SS, et al. Clinical characteristics of acute kidney injury in patients with glyphosate surfactant herbicide poisoning. Kidney Res Clin Pract. 2023;42(3):349–57.
207. Wunnapuk K, Gobe G, Endre Z, et al. Use of a glyphosate-based herbicide-induced nephrotoxicity model to investigate a panel of kidney injury biomarkers. Toxicol Lett. 2014;225(1):192–200.
208. Ulmeanu AI, Ghita I, Ulmeanu C. Neutrophil gelatinase-associated Lipocalin (NGAL) a promising biomarker for early detection of nephrotoxic injury. Rev Chim. 2020;71(2):15–21.
209. Abdul KSM, de Silva PMCS, Ekanayake EMDV, et al. Occupational Paraquat and glyphosate exposure may decline renal functions among rural farming communities in Sri Lanka. IJERPH. 2021;18(6):3278.
210. Yokota K, Fukuda M, Katafuchi R, Okamoto T. Nephrotic syndrome and acute kidney injury induced by malathion toxicity. BMJ Case Rep. 2017;2017:bcr-2017-220733.
211. Lebov JF, Engel LS, Richardson D, et al. Pesticide use and risk of end-stage renal disease among licensed pesticide applicators in the agricultural health study. Occup Environ Med. 2016;73(1):3–12.
212. Martin-Reina J, Casanova AG, Dahiri B, et al. Adverse health effects in women farmers indirectly exposed to pesticides. IJERPH. 2021;18(11):5909.
213. Chapman E, Haby MM, Illanes E, et al. Risk factors for chronic kidney disease of non-traditional causes: a systematic review. Rev Panam Salud Publica. 2019;43:1.
214. Jayasinghe S. Chronic kidney disease of unknown etiology should be renamed chronic agrochemical Nephropath. MEDICC Rev. 2014;16(2):72.
215. Wilke RA, Qamar M, Lupu RA, et al. Chronic kidney disease in agricultural communities. Am J Med. 2019;132(10):e727–32.
216. Özpolat Çakar N, Kutsal D, Kiran S. Pesticide exposure and chronic kidney disease among agricultural workers. Ankara Med J. 2020;20(3):761–72.
217. Yang B, Xie Y, Guo M, et al. Nephrotoxicity and Chinese herbal medicine. CJASN. 2018;13(10):1605–11.
218. Jain A, Olivero JJ. Herbal nephropathy. Methodist DeBakey Cardiovasc J. 2019;15(3):228.
219. Bashardoust B, Asgari M. Acute oxalate nephropathy associated with herbal remedies. J Nephropharmacol. 2022;11(2):e10482.
220. Anger EE, Yu F, Li J. Aristolochic acid-induced nephrotoxicity: molecular mechanisms and potential protective approaches. IJMS. 2020;21(3):1157.
221. Claure-Del Granado R, Espinosa-Cuevas M. Herbal Nephropathy. En: Silva Junior GB, Ferreiro Fuentes A, Nangaku M, Remuzzi G, Ronco C, editores. Contributions to nephrology. S. Karger AG; 2021. pp. 143–54.

222. Zhou Q, Jiang L, Su T, et al. Overview of aristolochic acid nephropathy: an update. Kidney Res Clin Pract. 2023;42(5):579–90.
223. Jadot I, Declèves AE, Nortier J, Caron N. An integrated view of Aristolochic acid nephropathy: update of the literature. IJMS. 2017;18(2):297.
224. Ban TH, Min JW, Seo C, et al. Update of aristolochic acid nephropathy in Korea. Korean J Intern Med. 2018;33(5):961–9.
225. Han J, Xian Z, Zhang Y, et al. Systematic overview of Aristolochic acids: nephrotoxicity, carcinogenicity, and underlying mechanisms. Front Pharmacol. 2019;10:648.
226. Kumar M, Sarma DK, Shubham S, et al. Environmental endocrine-disrupting chemical exposure: role in non-communicable diseases. Front Public Health. 2020;8:553850.
227. Jacobson MH, Wu Y, Liu M, et al. Serially assessed bisphenol A and phthalate exposure and association with kidney function in children with chronic kidney disease in the US and Canada: a longitudinal cohort study. Taal MW, editor. PLoS Med. 2020;17(10):e1003384.
228. Jiang S, Wang Y, Wang Z, et al. Bisphenol A and its alternatives bisphenol S and F exposure with serum uric acid levels, hyperuricemia, and gout prevalence among US adults: a nationally representative cross-sectional study. BMC Public Health. 2024;24(1):370.
229. Rancière F, Botton J, Slama R, et al. Exposure to Bisphenol A and Bisphenol S and incident type 2 diabetes: a case–cohort study in the French cohort D.E.S.I.R. Environ Health Perspect. 2019;127(10):107013.
230. Kataria A, Levine D, Wertenteil S, et al. Exposure to bisphenols and phthalates and association with oxidant stress, insulin resistance, and endothelial dysfunction in children. Pediatr Res. 2017;81(6):857–64.
231. Charytan DM, Wu W, Liu M, et al. Organic pollutant exposure and CKD: A chronic renal insufficiency cohort pilot study. Kidney Med. 2024;6(3):100778.
232. Meng X, Zhang J, Wang W, et al. Effects of nano- and microplastics on kidney: physicochemical properties, bioaccumulation, oxidative stress and immunoreaction. Chemosphere. 2022;288:132631.
233. La Porta E, Exacoustos O, Lugani F, et al. Microplastics and kidneys: an update on the evidence for deposition of plastic microparticles in human organs, tissues and fluids and renal toxicity concern. IJMS. 2023;24(18):14391.
234. Sun X, Zhang W, Wang Y, et al. Combined exposure to di(2-ethylhexyl) phthalate and polystyrene microplastics induced renal autophagy through the ROS/AMPK/ULK1 pathway. Food Chem Toxicol. 2023;171:113521.
235. Sanclemente E, Zea L. Detección precoz de enfermedades renales en escolares entre 12 a 18 años en cinco comunas de Santiago de Cali, Buenaventura y Popayán. Bogotá: Ministerio de Salud; 1996.
236. Suthar KS, Vanikar AV, Nigam LA, et al. Urinary screening for early detection of kidney diseases. Indian J Pediatr. 2018;85(8):607–12.
237. Chen TK, Coca SG, Estrella MM, et al. Longitudinal TNFR1 and TNFR2 and kidney outcomes: results from AASK and VA NEPHRON-D. JASN. 2022;33(5):996–1010.
238. Cho BS, Hahn WH, Cheong HI, et al. A nationwide study of mass urine screening tests on Korean school children and implications for chronic kidney disease management. Clin Exp Nephrol. 2013;17(2):205–10.
239. Macias Diaz DM, Corrales Aguirre MDC, Reza Escalera AL, et al. Histologic characterization and risk factors for persistent albuminuria in adolescents in a region of highly prevalent end-stage renal failure of unknown origin. Clin Kidney J. 2022;15(7):1300–11.

5 Nephropathy Due to Exogenous Poisoning

Alice Maria Costa Martins,
Gdayllon Cavalcante Meneses,
Polianna Lemos Moura Moreira Albuquerque,
Nicole Coelho Lopes, Igor Moreira de Almeida,
Leticia Machado de Araujo,
and Bruna Viana Barroso Martins

5.1 Introduction

Exogenous poisoning is understood as the contact of an organism with a substance that can trigger harmful reactions that may compromise the integrity of the victim, regardless this event is accidental or intentional [1–3]. In Brazil, in 2023, around 216,647 notifications of cases of exogenous poisoning were recorded. According to the DataSUS portal—Brazilian National Public Health System (2023), the agents responsible for the largest number of cases of poisoning are medications, drugs of abuse, household cleaning products, and pesticides. Kidney damage resulting from a large number of exogenous poisonings varies in severity, and it is a global public health problem. Interactions between these substances and the organism can produce relevant disorders, such as toxic acute kidney injury (AKI). Nonsteroidal anti-inflammatory drugs (NSAIDs), for example, can cause acute interstitial nephritis (AIN), characterized by an inflammatory response in the kidneys and changes in renal hemodynamics, which can lead to an acute decline in renal function [4, 5].

There are many examples to emphasize the misuse of therapeutical agents. Acetaminophen, which is safe in therapeutic doses, in an overdose can lead to severe mitochondrial dysfunction and oxidative stress, being a potential cause of acute tubular injury and, consequently, AKI [6–10]. Lithium carbonate, frequently used in the treatment of mood disorders, is associated with AIN and proximal tubular dysfunction, in addition to promoting fibrosis and chronic inflammation that, in the long term, can progress to chronic kidney disease (CKD). [11–13] Antiepileptic drugs such as carbamazepine and phenytoin, together with the antipsychotic clozapine, have the potential to cause AIN [14–16]. Tricyclic antidepressants can induce rhabdomyolysis, a syndrome that results in the release of myoglobin into the blood, which can cause AKI if not treated properly [17].

Some pesticides such as paraquat and glyphosate are known for their nephrotoxic effects, which include direct oxidative stress and mitochondrial dysfunction, impairing the ability of renal cells to generate energy, leading to cellular injury [18–22]. Insecticides such as organophos-

A. M. C. Martins (✉) · G. C. Meneses · N. C. Lopes
I. M. de Almeida · L. M. de Araujo · B. V. B. Martins
Programas de Pós-graduação em Desenvolvimento e Inovação Tecnológica de Medicamentos, Ciências Farmacêuticas e Farmacologia, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

P. L. M. M. Albuquerque
School of Medicine, Charles Darwin Universit,
Faculty of Health, Darwin, Australia
e-mail: polianna.albuquerque@cdu.edu.au

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_5

phates and carbamates can result in renal hypoperfusion, direct damage to the renal parenchyma, endothelial damage, inflammation, and rhabdomyolysis [23, 24]. Household cleaning agents, such as sodium lauryl sulfate-based detergents, can cause AIN through the deposition of oxalate crystals in the renal tubules, which can lead to tubular obstruction and inflammation [13, 25, 26]. Drugs of abuse such as alcohol have complex effects on the kidneys and can alter the renin-angiotensin system, generate hypertension, and cause glomerular dysfunction, which, in chronic cases, can progress to kidney disease [27]. Cocaine, which represents a global concern, is nephrotoxic through several mechanisms, including rhabdomyolysis and the development of distinct glomerulopathies, which can result in nephrotic syndrome and renal failure [12, 28]. Opioid substances such as heroin can cause glomerulopathies such as membranoproliferative glomerulosclerosis, which can lead to end-stage renal disease [25, 26]. In addition to conventional renal assessment tests such as creatinine, proteinuria, and urea, studies with unconventional biomarkers such as NGAL (neutrophil gelatinase-associated lipocalin), KIM-1 (kidney injury molecule 1), IL-18 (interleukin 18), and TNFR-1 (tumor necrosis factor receptor 1) have shown promise for improving early detection of cases with an unfavorable prognosis that may progress to renal failure and death [29, 30].

Due to these different contexts caused by specific agents, in-depth understanding of renal involvement is crucial for the development of preventive and therapeutic strategies. In addition, studies with biomarkers for early identification of signs of renal toxicity are vital for effective intervention, which may include everything from cessation of exposure to the toxic substance to renal replacement therapy, such as dialysis, in situations of severe renal injury.

5.2 Medicines

Currently, Brazil is among the largest consumers of medicines in the world and the largest among tropical countries [31]. In 2017, the date of the last record in the National System of Toxic-Pharmacological Information (SINITOX), medicines have represented the main cause of exogenous poisoning (27.11% of cases) and the second largest cause of deaths due to poisoning (25% of cases), with an increasing trend compared to previous years [32]. These data may be underrated, and they are under review; possibly, the problem is bigger than it is reported.

Acute poisonings due to medicines have been increasing in recent years, mainly due to irrational use and given the relatively easy accessibility in the country in a scenario of expansion of e-commerce in pharmaceutical retail after the change in behavior with the COVID-19 pandemic [33, 34]. Data from the Notifiable Injuries Information System (SINAN, Sistema Nacional de Agravos de Notificacao, Health Ministry of Brazil) reveal that, among the circumstances, accidents and suicide attempts account for the majority of cases, with emphasis on over-the-counter (OTC) medications, including analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), and antipsychotics. In parallel, antibiotics, antihypertensives, and immunosuppressants are the main causes of hospital poisoning [32, 34–37].

Drug poisoning occurs when a medication, in doses above the therapeutically recommended dose or for a prolonged period, is administered or comes into contact with the body, causing clinical manifestations, including kidney injury [38, 39]. As the main route of clearance for most drugs, the kidney is one of the organs most affected by the direct or indirect toxicity of these substances, which can trigger AKI and even CKD and terminal chronic renal failure [40].

Drugs can cause renal injury through several mechanisms [38]: direct cytotoxicity of the drug (e.g., aminoglycosides, colistin, and amphotericin B), immunological effects related to the drug (e.g., beta-lactams, NSAIDs and checkpoint inhibitors), insolubility and crystallization of the drug in urine (e.g., methotrexate, acyclovir, and sulfadiazine), and alteration of cellular transporters (e.g., tenofovir and cisplatin) [38].

Kidney tubular cells, especially in the proximal segment, are highly susceptible to drug

injury due to their function of concentrating, reabsorbing, and secreting substances from the glomerular filtrate [38, 40]. Cationic drugs, such as aminoglycosides, can accumulate in cells by binding to the membrane and being endocytosed, leading to cellular damage when they exceed a certain threshold. Similarly, substances such as tenofovir and cisplatin are transported into cells by specific transporters and released in the urine, but high concentrations or failures in these transporters can also result in cytoplasmic accumulation. This accumulation and interference with cellular transporters can cause dose-dependent damage, affecting hydroelectrolytic balance, damaging mitochondrial DNA, increasing the production of free radicals, and inducing cellular apoptosis [38, 41–43].

Inflammatory reaction and tissue fibrosis in the glomeruli, proximal tubules, and interstitial cell matrix are a common cause of drug-induced nephrotoxicity, but it is difficult to diagnose, being confirmed only by biopsy and clinical history [42]. Only a minority of patients present the classic triad of symptoms (skin rash, fever, and eosinophilia), and AKI can develop up to months after the start of drug treatment, in the form of glomerulonephritis associated with proteinuria, when caused by an inflammatory response of the innate immune system, or in the form of acute or chronic interstitial nephritis, which is a type IV hypersensitivity reaction mediated by T cells [44]. Initially, the drugs act as haptens or prohaptens, binding to renal proteins and forming neoantigens, which are captured by macrophages and dendritic cells and then presented to T lymphocytes. Then, the renal interstitium is taken over by an inflammatory infiltrate, causing tissue damage [44, 45]. Drugs capable of triggering the inflammatory process in the kidneys include analgesics and NSAIDs, some antibiotics such as rifampicin, calcineurin inhibitors (cyclosporine and tacrolimus), lithium, and certain chemotherapeutic agents [42, 45].

Antipsychotic drug-induced nephropathy is a significant complication resulting from the abuse of these drugs. Among the associated renal disorders, rhabdomyolysis stands out, a pathological process caused by the lysis of skeletal muscle fibers that results in the release of intracellular contents, such as myoglobin and creatine kinase, into the bloodstream. Antipsychotics, particularly when used in high doses or inappropriately, are among the drugs most frequently associated with this phenomenon. The myoglobin released in the process can accumulate in the kidneys, obstructing the renal tubules and exerting a direct cytotoxic effect, which can culminate in acute tubular necrosis. Such damage is exacerbated by the consequent reduction in the glomerular filtration rate (GFR), increasing the risk of AKI [46, 47].

5.3 Pesticides

Poisonings due to pesticides are a huge problem in Brazil with negative impacts on acute and chronic human health with immeasurable loss. While Brazil has been on the bandwagon of chemical input-intensive agricultural development for a long time, there has been a rapid increase in legalization of highly toxic pesticides in Brazil since 2016 and especially since 2019 [48].

Pesticides have a significant impact on public health and are classified as the third leading cause of suicide in Brazil [48]. According to data from the Ministry of Health [50], the country recorded 124,295 cases of pesticide poisoning between January 2013 and June 2022, affecting more men (65%) and occurring due to unintentional causes (47%). Among the regions of the country, the Southeast and South are the ones that record the most cases of exogenous pesticide poisoning [51].

Pesticides are products and agents with physical, chemical, or biological action used in nature with the aim of preserving it from possible damage caused by living beings, aiding in the productivity and economic development of agriculture [52–54]. These substances have a significant nephrotoxic potential in cases of poisoning, including the need for renal replacement therapy in up to 96% of cases [53, 55].

Organophosphates (OPs) are widely used in agricultural activities and pose a risk to the popu-

lation because they are irreversible inhibitors of acetylcholinesterase and can cause several clinical manifestations in exposed individuals, according to substance [21, 56]. In in vivo studies, the relationship between OPs and nephrotoxicity has already been described in substances such as methyl parathion and malathion, while clinical studies have shown that exposure to this chemical class can increase the risk of acute renal failure by 6.17 times, influencing the increase in the number of deaths. Furthermore, the nephrotoxicity of OPs has also been described as a factor that favors the development of CKD [57]. The pathophysiological mechanism of AKI in this scenario has not been fully elucidated, but it is known that the exposure time and concentration of the substance can negatively influence renal damage [56]. Studies suggest the occurrence of oxidative stress, rhabdomyolysis, hypovolemia, and direct tissue toxicity, as well as renal hypoperfusion and interference in the excretion of electrolytes that partially occur due to cholinergic mechanisms, contributing to the decline in renal function [56, 57].

The histopathology of nephrotoxicity by OP demonstrates alterations such as glomerular shrinkage, inflammatory cell infiltration, vascular alteration, rupture of Bowman's capsule, cytoplasmic degeneration of renal tubules, and even tubular necrosis [56]. There are studies reporting that OP poisoning can result in increases in urea and creatinine levels, as well as changes in urinary output and a significant reduction in the action of antioxidant enzymes [21, 56].

However, organochlorines (OC) also constitute a chemical class of pesticides that were widely used until they were banned in several countries, but they can still be present in nature due to their long half-life, lipophilicity, and easy access [58–60]. Among the systemic complications observed in OC poisoning, AKI and CKD are important [58, 60]. In this scenario, oxidative stress is believed to play an important role in the pathogenesis, and this occurs mainly with the accumulation of OC in the tissue due to the low excretory capacity in CKD, which may contribute to the appearance of clinical manifestations, such as changes in GFR, proteinuria, tubular injury, tubulointerstitial fibrosis, and renal dysfunction [58, 59]. Thus, supportive treatment, hydration, and correction of acid-base balance are important management strategies to reduce the risk of developing AKI in these patients [60].

Kidney biomarkers such as NGAL and KIM-1 were evaluated in cases of paraquat poisoning as early indicators of kidney injury [61]. While urinary NGAL increased in patients with AKI after 24 hours, KIM-1 showed no significant difference between the groups. Both NGAL and KIM-1 increased between 24 and 48 hours after exposure to paraquat, regardless of the occurrence of AKI. The study demonstrates that paraquat strongly stimulates the expression of NGAL and KIM-1, suggesting that NGAL may reflect renal injury by reactive oxygen species. Contrary to expectations, NGAL did not stand out as an early marker to predict AKI, but its increase after 72 h may indicate the severity of renal injury [61].

5.4 Chemicals

Chemical substances present in our daily lives are found in the air, in the soil, or in products that are routinely used at home or in industry [62]. However, concentrations of certain substances above those permitted and improper use can cause serious problems, both for the environment and around public health. Regulatory Standard 14,725–1 of 2009 defines a dangerous chemical product as one that is classified as an agent capable of exceeding the safety limit, leading to cases of acute or chronic poisoning, mutagenicity, or death [63].

According to the World Health Organization (WHO), more than 70% of the population is unintentionally poisoned by some type of chemical product [64]. Ten chemical agents of greatest clinical relevance in public health were listed, including air contaminants, arsenic, asbestos, benzene, cadmium, dioxins and similar compounds, fluoride, lead, mercury, and pesticides [65]. In the Brazilian scenario, the WHO classifies the country as one of the most susceptible to the occurrence of exogenous poisoning events [64], which is corroborated by reports published

by SINITOX, where almost 4% of the population was affected by exogenous poisoning from chemical products, and, in addition to the cases caused by heavy metals and household cleaning agents, this number increases to approximately 10% [32]. The damage observed ranges from skin and mucous membrane irritations to systemic complications, such as cardiovascular, endothelial, respiratory, and renal damage.

Toxic alcohols, in addition to ethanol, can be found as fuel adulterants and as contaminants in clandestine beverage factories, such as methanol, or in the production of resins, paints, and varnishes, such as ethylene glycol, which can also be used to cool combustion engines [66]. Contamination by these substances can be accidental or intentional (in cases of suicide, when ethylene glycol is used together with ethanol or as a substitute for it) [67].

In methanol poisoning, although quite considerable, there are few studies regarding the renal system. Its metabolic pathway involves biotransformation into formaldehyde with consequent formation of formic acid, progressing to metabolic acidosis [68], characterized by an exacerbated anion gap that, in addition to lesions in the central nervous system and optic nerve, leads to changes in multiple organs, causing hypotension, acute renal failure, rhabdomyolysis, hypomagnesemia, and hypokalemia, among others [66].

Regarding ethylene glycol, its metabolism results from the increase in plasma levels of this alcohol due to its rapid absorption, resulting in increasing metabolic acidosis and anion gap arising from excess lactic acid, and metabolism, which occurs through the action of the enzymes alcohol and aldehyde dehydrogenases, which promote the formation of glycolic acid, which will later be transformed into glyoxylic acid and then into oxalic acid [67], which precipitates as insoluble crystals of calcium oxalate, which can be deposited in various tissues and, thus, induce acute renal failure and hypocalcemia [66].

Lethal isopropyl alcohol poisoning, although little discussed, occurs due to an osmolar imbalance, due to its biotransformation into acetone, in addition to the fact that none of its metabolites are organic, which can lead to an erroneous assessment of serum creatinine concentration, leading to a false prognosis of renal failure [69].

Heavy metals are extremely important when it comes to kidney toxicity and are widely used in the industrial and agricultural sectors. They pose health risks when ingested and inhaled, when they encounter the skin, or accidentally, such as through inadequate therapeutic measures. The main targets involved in the reabsorption of heavy metals are the apical membrane of the first zone of the proximal tubule, the loop of Henle, and the renal segments [70], and their mechanism of action will generally depend on the concentration, type, and how these heavy metals are found in the body, whether in their free or conjugated form, factors that differentiate whether renal failure is acute or chronic [69].

Acute heavy metal poisoning is induced by the ionized form of the agents, which cause direct cellular damage, rupture of the cell membrane, and uncoupling of the respiratory tract, releasing signals of apoptosis (cytokines and reactive oxygen species), while in chronic poisoning, it is observed that the inert form of the metal bound to proteins is conjugated with metallothionein and glutathione, which are consequently reabsorbed by endocytosis in the proximal tubule, which can cause chronic inflammation, fibrosis, and renal failure [70]. Despite the general mechanism, some metals have particularities in their pathways of action, such as mercury, which causes enzyme inhibition and changes in cell membranes due to reactions with chemical groups [66], thus increasing its affinity for renal tissue, generating nephrotic syndrome [71] and cadmium, which upon entering the body, in addition to the mechanisms of apoptosis and oxidative stress, is transported through the bloodstream by erythrocytes and albumin, depositing in various organs, such as the kidney [72].

Other chemicals, despite their more pronounced toxic effects being observed in other tissues and organs of the body, also affect the renal system, such as carbon monoxide, household cleaning compounds, and other corrosive agents, which induce inflammatory processes and oxidative stress, causing apoptosis and ischemia [66, 73].

5.5 Drugs of Abuse

The WHO defines "a drug as any chemical entity or mixture of entities that alters the biological function and possibly the structure of the organism." Specifically, drugs of abuse are a class of psychoactive substances derived from various natural or synthetic compounds that act on the nervous system, altering functions that regulate sensations and behaviors and triggering different mechanisms of dependence and tolerance to the drug [74].

According to the report by the United Nations Office on Drugs and Crime (UNDOC, 2023), the consumption of drugs of abuse has grown exponentially in the last decade, leading to an increase in associated clinical and subclinical complications. The main classes of drugs of abuse include opioids, central nervous system depressants, stimulants, and psychedelic agents [75].

Drugs in general are nephrotoxic in high and/or repeated doses, and this is due to the physiological nature of the kidney to filter and detoxify the body [76]. Renal overload triggers several direct and indirect mechanisms, such as inflammation and necrosis, due to the formation or accumulation of toxic xenobiotics or biotransformation products that lead to kidney damage to varying degrees and intensities [77]. Therefore, renal involvement by drugs of abuse is multifactorial and is directly correlated with the sensitivity of the exposed individual and the exposure profile to the drug, including the chemical nature of the substance. Cocaine use can result in skeletal muscle ischemia, followed by rhabdomyolysis, an important cause of primary renal damage [78]. Drug abuse can trigger renal infarctions and renal atherosclerosis, through mechanisms similar to myocardial infarction, which in the short term cause AKI and, when associated with long-term use, can progress to CKD [79]. This is due to oxidative stress and GFR overload caused directly by cocaine and indirectly by nephrotoxic secondary metabolites of the drug such as ecgonine methyl ester and benzoylecgonine [80]. The renal diagnosis of cocaine abuse initially consists of identifying which other possible agents may be involved in the intoxication, due to the high rate of concomitant intoxication by more than one agent, and checking renal function by measuring cystatin C, analyzing the creatinine clearance rate and proteinuria [81].

The use of crack cocaine, a smokable form of cocaine, has been associated with several kidney diseases. Studies indicate that crack cocaine can cause rhabdomyolysis, a condition in which there is rapid destruction of skeletal muscle tissue that releases substances such as myoglobin into the bloodstream, potentially causing acute kidney failure. In addition, crack cocaine use can lead to glomerular diseases, such as glomerulonephritis, resulting from inflammation of the kidney glomeruli. Increased blood pressure, a common consequence of cocaine use, can also damage the blood vessels of the kidneys over time. Other problems include renal ischemia, due to vasoconstriction that reduces blood flow to the kidneys, and acute tubular necrosis, where cells in the kidney tubules die. These cumulative effects can lead to chronic kidney disease or kidney failure. Therefore, it is crucial to consider the use of substances such as crack in patients with kidney problems to ensure proper diagnosis and treatment [84].

Acute opioid poisoning, in this case heroin, follows the triad of miosis, respiratory depression, and coma [85]. At the renal level, the most reported renal involvement in the literature, as well as cocaine, is atraumatic rhabdomyolysis, which manifests clinically with myalgias, myoglobinuria, and elevated serum creatine kinase [86, 87]. In addition, heroin abuse can lead to nephrotic syndrome due to glomerulopathies. Regarding the mechanism, what occurs is a disarray in the walls of the glomerular capillaries, resulting in increased permeability to plasma proteins. When this damage involves only a part of each affected glomerulus, it is called focal segmental glomerulosclerosis [88]. This condition consists of sclerosis of some glomeruli, generating an increase in the mesangial matrix, obliteration of the capillary lumen, hyaline deposits, and foamy macrophages in the affected glomeruli, in a progressive manner and indicated in the literature as underlying episodes of heroin abuse [88].

Table 5.1 Nephropathies and mechanisms associated with different exogenous poisonings by synthetic agents

Agent type	Nephropathies and associated mechanisms	References
NSAIDs	Acute interstitial nephritis, renal hemodynamic changes	[19, 20]
Acetaminophen	Severe mitochondrial dysfunction, oxidative stress, acute tubular injury	[21–25]
Lithium carbonate	Acute interstitial nephritis, proximal tubular dysfunction, fibrosis and chronic inflammation	[26–28]
Antiepileptic medications (carbamazepine, phenytoin) and antipsychotic (clozapine)	Acute interstitial nephritis	[29–31]
Tricyclic antidepressants	Rhabdomyolysis	[32]
Pesticides (paraquat, glyphosate)	Oxidative stress, mitochondrial dysfunction, renal tubular damage, and increased urinary NGAL and KIM-1	[33–36]
Insecticides (organophosphates, carbamates)	Kidney hypoperfusion, direct damage to renal parenchyma, inflammation, rhabdomyolysis	[37, 38]
Household cleaning agents	Acute interstitial nephritis due to deposition of calcium oxalate crystals in the renal tubules	[28, 39, 40]
Alcohol	Alteration of the renin-angiotensin system, hypertension, glomerular dysfunction	[41]
Cocaine	Rhabdomyolysis, development of distinct glomerulopathies	[29–31]
Opioids (heroin)	Glomerulopathies such as membranoproliferative glomerulosclerosis	[32, 33]

Diagnosis consists of evaluating renal function with differential analysis for rhabdomyolysis and nephrotic syndrome, including measurement of serum creatine kinase and creatinine and imaging tests in cases of suspected glomerulopathy. In clinical management, the administration of an opioid antagonist such as naloxone and implementation of therapies to support renal function are recommended, depending on the severity, which may range from electrolyte replacement to dialysis [89].

Alcohol consumption, low-dose alcoholism, has a nephroprotective effect, evidenced by the increased activity of antioxidant enzymes such as glutathione peroxidase [90–92]. However, abuse or recurrent use of alcohol can contribute to kidney damage, with increased lipid peroxidation in renal tissue, accompanied by morphological changes such as renal tubular necrosis and interstitial nephritis [93, 94]. Alcohol is metabolized mainly by three different pathways, the main dehydrogenase pathway, via the microsomal ethanol oxidative system, and via peroxidase-catalase, generating toxic metabolites, which in excess exacerbate the kidney's ability to filter them, generating an accumulation in the glomerulus leading to possible AKI. Diagnosis is made based on the patient's clinical history of alcohol use and abuse and the individual's renal function profile [66].

Table 5.1 summarizes the mechanisms associated with different exogenous poisonings causing nephropathies.

5.6 Conclusion

Exogenous poisoning has become a hot topic in public health and may cause significant impacts on health systems, including increased mortality and morbidity, with associated nephropathies. Medications, drugs of abuse, pesticides, and household chemicals are important toxic agents, which lead to a wide range of kidney impairments, from acute kidney injury to chronic kidney disease. Studies with advanced biomarkers for early detection may assist in effective intervention and improve preventive and therapeutic strategies to mitigate the impacts on public health and improve renal prognosis in these cases of poisoning.

5.7 Take-Home Message

- Provide ongoing practical training for health professionals on the management of nephropathies resulting from exogenous poisoning, using basic diagnostic techniques and accessible treatments.
- Develop and implement simple screening protocols for the early identification of kidney injuries caused by poisoning, based on easily observable clinical signs and symptoms.
- Conduct awareness campaigns to inform the population about the risks and prevention of poisoning by medications, cleaning products, pesticides, and drugs of abuse, emphasizing the importance of safe use.
- Ensure access to basic renal support treatments and promote the use of renal biomarkers, such as NGAL and KIM-1, for the early detection of kidney injuries.
- Establish partnerships with international organizations and academic institutions to share knowledge, resources, and best practices, helping to implement training programs and provide appropriate medical equipment.

References

1. Neto J, Castro T, Silva H, Almeida C, Filho J, Cantão B, et al. Epidemiological characterization of exogenous poisoning cases in the state of Pará between 2012 and 2021. Rev Enferm UFPI [Internet]. 2023;12(1)
2. BRASIL. Ministério da Saúde. DATASUS. Tabnet. Ministério da Saúde. Brasília, DF: Ministério da Saúde; 2022.
3. Albuquerque P, Meneses G. Toxin-related acute kidney injury. In: Nephrology and Public Health Worldwide [Internet]; 2021. p. 131–42. Available from: https://www.karger.com/Article/FullText/517699.
4. Radi ZA, Khan KN. Cardio-renal safety of nonsteroidal anti-inflammatory drugs. J Toxicol Sci. 2019;44(6):373–91.
5. Jeon Y, Lis JB, Chang WG. NSAID associated bilateral renal infarctions: a case report. Int J Nephrol Renovasc Dis. 2019;12:177–81.
6. Park BK, Dear JW, Antoine DJ. Paracetamol (acetaminophen) poisoning. BMJ Clin Evid [Internet]. 2015;2015. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26479248
7. Hinson JA, Roberts DW, James LP. Mechanisms of acetaminophen-induced liver Necrosis. In Handb Exp Pharmacol. 2010:369–405.
8. Vliegenthart ADB, Shaffer JM, Clarke JI, Peeters LEJ, Caporali A, Bateman DN, et al. Comprehensive microRNA profiling in acetaminophen toxicity identifies novel circulating biomarkers for human liver and kidney injury. Sci Rep. 2015;5(1):15501.
9. Azab AN, Shnaider A, Osher Y, Wang D, Bersudsky Y, Belmaker RH. Lithium nephrotoxicity. Int J Bipolar Disord. 2015;3(1):13.
10. Leal S, Ricardo Jorge DO, Joana B, Maria SS, Isabel SS. Heavy alcohol consumption effects on blood pressure and on kidney structure persist after long-term withdrawal. Kidney Blood Press Res. 2017;42(4):664–75.
11. Goel N, Pullman JM, Coco M. Cocaine and kidney injury: a kaleidoscope of pathology. Clin Kidney J. 2014;7(6):513–7.
12. Filho JCCL, Ogawa MY, de Souza Andrade TH, de Andrade Cordeiro Gadelha S, Fernandes PFCBC, Queiroz AL, et al. Spectrum of acute kidney injury associated with cocaine use: report of three cases. BMC Nephrol. 2019;20(1):99.
13. Barutta F, Bruno G, Mastrocola R, Bellini S, Gruden G. The role of cannabinoid signaling in acute and chronic kidney diseases. Kidney Int. 2018;94(2):252–8.
14. Koga S, Kimata T, Yamanouchi S, Tsuji S, Yoshimura K, Araki A, et al. Risk factors for sodium valproate-induced renal tubular dysfunction. Clin Exp Nephrol. 2018;22(2):420–5.
15. Davis EAK, Kelly DL. Clozapine-associated renal failure: a case report and literature review. Mental Health Clin. 2019;9(3):124–7.
16. Mohamed F, Endre ZH, Pickering JW, Jayamanne S, Palangasinghe C, Shahmy S, et al. Mechanism-specific injury biomarkers predict nephrotoxicity early following glyphosate surfactant herbicide (GPSH) poisoning. Toxicol Lett. 2016;258:1–10.
17. Roberts DM, Wilks MF, Roberts MS, Swaminathan R, Mohamed F, Dawson AH, et al. Changes in the concentrations of creatinine, cystatin C and NGAL in patients with acute paraquat self-poisoning. Toxicol Lett. 2011;202(1):69–74.
18. Mohamed F, Buckley NA, Jayamanne S, Pickering JW, Peake P, Palangasinghe C, et al. Kidney damage biomarkers detect acute kidney injury but only functional markers predict mortality after paraquat ingestion. Toxicol Lett. 2015;237(2):140–50.
19. Nakayama T, Mimura Y, Hirano K. Renal cortical hypoperfusion caused by glyphosate–surfactant herbicide. Clin Exp Nephrol. 2019;23(6):865–6.
20. Lamb T, Selvarajah LR, Mohamed F, Jayamanne S, Gawarammana I, Mostafa A, et al. High lethality and minimal variation after acute self-poisoning with carbamate insecticides in Sri Lanka—implications for global suicide prevention. Clin Toxicol. 2016;54(8):624–31.

21. Lee FY, Chen WK, Lin CL, Lai CY, Wu YS, Lin IC, et al. Organophosphate poisoning and subsequent acute kidney injury risk. Medicine. 2015;94(47):e2107.
22. Gawarammana IB, Ariyananda PL, Palangasinghe C, De Silva NGL, Fernando K, Vidanapathirana M, et al. Emerging epidemic of fatal human self-poisoning with a washing powder in southern Sri Lanka: a prospective observational study. Clin Toxicol. 2009;47(5):407–11.
23. Dassanayake U, Gnanathasan C. Acute renal failure following oxalic acid poisoning: a case report. J Occup Med Toxicol. 2012;7(1):17.
24. Tsujihata M. Mechanism of calcium oxalate renal stone formation and renal tubular cell injury. Int J Urol. 2008;15(2):115–20.
25. Gully M, Frauger É, Spadari M, Pochard L, Pauly V, Romain F, et al. Effets uro-néphrologiques des produits utilisés par les usagers de drogues : revue de la littérature et enquête pharmaco-épidémiologique en France et dans la région de Marseille. Nephrol Ther. 2017;13(6):429–38.
26. Pendergraft WF, Herlitz LC, Thornley-Brown D, Rosner M, Niles JL. Nephrotoxic effects of common and emerging drugs of abuse. Clin J Am Soc Nephrol. 2014;9(11):1996–2005.
27. Fan Z, Yun J, Yu S, Yang Q, Song L. Alcohol consumption can be a "double-edged sword" for chronic kidney disease patients. Med Sci Monit. 2019;25:7059–72.
28. Nanavati A, Herlitz LC. Tubulointerstitial injury and drugs of abuse. Adv Chronic Kidney Dis. 2017;24(2):80–5.
29. Barnett LMA, Cummings BS. Nephrotoxicity and renal pathophysiology: a contemporary perspective. Toxicol Sci. 2018;164(2):379–90.
30. Kashani K, Kellum JA. Novel biomarkers indicating repair or progression after acute kidney injury. Curr Opin Nephrol Hypertens. 2015;24(1):21–7.
31. IQVIA Institute for Human Data Science. Global Use of Medicines: Outlook to 2028, January 2024 [Internet]; 2024. Available from: www.iqviainstitute.org
32. BRASIL. Ministério da Saúde. SINITOX - Sistema Nacional de Informações Tóxico-Farmacológicas [Internet]. Ministério da Saúde. Manguinhos, RJ: Fundação Oswaldo Cruz; 2009. Available from: https://sinitox.icict.fiocruz.br/dados-nacionais
33. Borba H, Carvalho D. Consumer behavior of pharmaceutical drugs and services: current challenges and post-Covid-19 horizons. Revista Saúde e Desenvolvimento Humano. 2021;9(3):1–12.
34. Domingues PHF, Galvão TF, de Andrade KRC, de Sá PTT, Silva MT, Pereira MG. Prevalence of self-medication in the adult population of Brazil: a systematic review. Rev Saude Publica. 2015;49
35. Sereno VMB, Silva AS, Silva GC. Perfil epidemiológico das intoxicações por medicamentos no Brasil entre os anos de 2013 a 2017. Braz J Dev. 2020;6(6):33892–903.
36. Almeida ABM, Uchoa GF, Carvalho AMR, Vasconcelos LF, Medeiros DS, Cavalcante MG. Epidemiologia das intoxicações medicamentosas registradas no Sistema Nacional de Informações Tóxico-Farmacológicas de 2012-2016. Saúde e Pesquisa. 2020;13(2):431–40.
37. Duarte FG, de Paula MN, Vianna NA, de Almeida MCC, Junior EDM. Óbitos e internações decorrentes de intoxicações por medicamentos com prescrição e isentos de prescrição, no Brasil. Rev Saude Publica. 2021;55:81.
38. Perazella MA. Pharmacology behind common drug nephrotoxicities. Clin J Am Soc Nephrol. 2018;13:1897–908.
39. Rangel NL, Francelino EV. Caracterização do Perfil das Intoxicações Medicamentosas no Brasil, durante 2013 a 2016. ID on line Revista de Psicologia. 2018;12(42):121–35.
40. Wu H, Huang J. Drug-induced nephrotoxicity: pathogenic mechanisms, biomarkers and prevention. Strategies. 2018:559–67.
41. Lopez-novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int [Internet]. 2011;79(1):33–45. https://doi.org/10.1038/ki.2010.337.
42. Kwiatkowska E, Domański L, Dziedziejko V, Kajdy A, Stefańska K, Kwiatkowski S. The mechanism of drug nephrotoxicity and the methods for preventing kidney damage. Int J Mol Sci. 2021;22(11):6109.
43. Sales GTM, Foresto RD. Drug-induced nephrotoxicity. Rev Assoc Med Bras. 2020;66(suppl 1):s82–90.
44. Perazella MA, Rosner MH. Drug-induced acute kidney injury. Clin J Am Soc Nephrol. 2022;17(8):1220–33.
45. Perazella MA. Drug-induced acute kidney injury: diverse mechanisms of tubular injury. Curr Opin Crit Care. 2019;25(6):550–7.
46. Morales-Alvarez MC. Nephrotoxicity of antimicrobials and antibiotics. Adv Chronic Kidney Dis. 2020;27(1):31–7.
47. Naughton CA. Drug-induced nephrotoxicity. Am Fam Physician. 2008;78(6):743–50.
48. Ollinaho OI, Pedlowski MA, Kröger M. Toxic turn in Brazilian agriculture? The political economy of pesticide legalisation in post-2016 Brazil. Third World Q. 2023;44(3):612–30.
49. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Relatório Nacional de Vigilância em Saúde de Populações Expostas a Agrotóxicos, vol. 1., Departamento de Vigilância em Saúde Ambiental e Saúde do Trabalhador. Brasília, DF: Ministério da Saúde; 2018.
50. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde e Ambiente. Intoxicações exógenas por agrotóxicos no Brasil—2013 a 2022 [Internet], vol. 54. Brasília, DF: Boletim Epidemiológico; 2023. Available from: www.saude.gov.br
51. da Silva LLM, Garrido RG. Organofosforados e organoclorados: toxicologia médica e reflexos ambientais. Res Soc Dev. 2021;10(10):e313101018853.
52. BRASIL. Decreto Nº 4.074, de 4 de janeiro de 2002. Regulamenta a Lei no- 7.802, de 11 de julho de 1989,

que dispõe sobre a pesquisa, a experimentação, a produção, a embalagem e rotulagem, o transporte, o armazenamento, a comercialização, a propaganda comercial, a utilização, a importação, a exportação, o destino final dos resíduos e embalagens, o registro, a classificação, o controle, a inspeção e a fiscalização de agrotóxicos, seus componentes e afins, e dá outras providências, vol. 139. Diário Oficial da União; 2002.
53. He M, Wu Y, Xie Z, Li Z, Hao L, Liu G, et al. Epidemiology of hospitalizations due to pesticide intoxication-associated acute kidney injury in China. Int Urol Nephrol. 2022;54(2):377–83.
54. Ramos MLH, Lima V d S, Silva RE d, Nunes JV d N, Silva GC d. Perfil epidemiológico dos casos de intoxicação por agrotóxicos de 2013 a 2017 no Brasil. Braz J Dev. 2020;6(7):43802–13.
55. Albuquerque P, Meneses G. Toxin-related acute kidney injury. Contrib Nephrol. 2021;199:131–42.
56. Georgiadis G, Mavridis C, Belantis C, Zisis IE, Skamagkas I, Fragkiadoulaki I, et al. Nephrotoxicity issues of organophosphates. Toxicology. 2018;406–407:129–36.
57. Sobolev VE, Sokolova MO, Jenkins RO, Goncharov NV. Molecular mechanisms of acute organophosphate nephrotoxicity. Int J Mol Sci. 2022;23(16):8855.
58. Ghosh R, Siddarth M, Singh N, Tyagi V, Kare PK, Banerjee BD, et al. Organochlorine pesticide level in patients with chronic kidney disease of unknown etiology and its association with renal function. Environ Health Prev Med. 2017;22(1):49.
59. Siddarth M, Datta SK, Mustafa MD, Ahmed RS, Banerjee BD, Kalra OP, et al. Increased level of organochlorine pesticides in chronic kidney disease patients of unknown etiology: role of GSTM1/GSTT1 polymorphism. Chemosphere. 2014;96:174–9.
60. Hanif S, Sattar RA. Frequency of acute kidney injury (AKI) among patients presenting with organophosphate poisoning at National Poison Control Centre, Karachi: a prospective cross-sectional survey. Pak J Med Sci. 2022;38(3)
61. Gil HW, Yang JO, Lee EY, Hong SY. Clinical implication of urinary neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 in patients with acute paraquat intoxication. Clin Toxicol. 2009;47(9):870–5.
62. World Health Organization. Chemical safety/Public health concern [Inernet]. Available from: https://www.who.int/health-topics/chemical-safety. Accessed at: 03/20/2024.
63. ASSOCIAÇÃO BRASILEIRA DE NORMAS TÉCNICAS. NBR 14725-1: Produtos químicos — Informações sobre segurança, saúde e meio ambiente Parte 1: Terminologia. Rio de Janeiro; 2009. p. 6.
64. World Health Organization. The public health impact of chemicals: knowns and unknowns – data addendum for 2019. World Health Organization; 2021. p. 1–4.
65. World Health Organization. 10 Chemicals of Public Health Concern [Internet]. Available from: https://www.who.int/news-room/photo-story/photo-story-detail/10-chemicals-of-public-health-concern. Accessed at: 03/20/2024.
66. São Paulo. Secretaria Municipal de Saúde. Coordenadoria de Vigilância em Saúde. Manual de Toxicologia Clínica: Orientações para assistência e vigilância das intoxicações agudas. São Paulo, SP: Núcleo de Prevenção e Controle das Intoxicações; 2017.
67. Ahmad Y, Kissling S, Torrent C, Chiche JD, Liaudet L, Ltaief Z. The three biological gaps and hyperoxaluria in ethylene glycol poisoning: case presentation and review. Eur Rev Med Pharmacol Sci. 2021;25(20):6295–9.
68. Chang ST, Wang YT, Hou YC, Wang IK, Hong HH, Weng CH, et al. Acute kidney injury and the risk of mortality in patients with methanol intoxication. BMC Nephrol. 2019;20(1):205.
69. Petejova N, Martinek A, Zadrazil J, Teplan V. Acute toxic kidney injury. Ren Fail. 2019;41(1):576–94.
70. Lentini P, Zanoli L, Granata A, Signorelli SS, Castellino P, Dellaquila R. Kidney and heavy metals – the role of environmental exposure. Mol Med Rep. 2017;15(5):3413–9.
71. Yawei S, Jianhai L, Junxiu Z, Xiaobo P, Zewu Q. Epidemiology, clinical presentation, treatment, and follow-up of chronic mercury poisoning in China: a retrospective analysis. BMC Pharmacol Toxicol. 2021;22(1):25.
72. Genchi G, Sinicropi MS, Lauria G, Carocci A, Catalano A. The effects of cadmium toxicity. Int J Environ Res Public Health. 2020;17(11):3782.
73. Wei KY, Liao CY, Chung CH, Lin FH, Tsao CH, Sun CA, et al. Carbon monoxide poisoning and chronic kidney disease risk: a nationwide, population-based study. Am J Nephrol. 2021;52(4):292–303.
74. BRASIL. Ministério da Saúde. Glossário Saúde Brasil/Substâncias Psicoativas: substâncias capazes de produzir alterações no sistema nervoso central [Internet]. Available from: https://www.gov.br/saude/pt-br/assuntos/saude-brasil/glossario/substancias-psicoativas. Accessed at: 03/20/2024.
75. Swift RM, Lewis DC. Farmacologia da dependência e abuso de drogas. In: Golan DE, et al., editors. Princípios de farmacologia: a base fisiopatológica da farmacoterapia. 2nd ed. Rio de Janeiro: Guanabara Koogan; 2009. p. 265–6.
76. Pinto PS, Carminatti M, Lacet T, Rodrigues DF, Nogueira LO, Bastos MG, et al. Insuficiência renal aguda nefrotóxica: prevalência, evolução clínica e desfecho. J Bras Nefrol. 2009;31(3):183–9.
77. Martins C, Younes-Ibrahim M. Nefrotoxicidade – aspectos básicos. Med Ciên e Arte. 2022;1(4):31–44.
78. Carrasco R, Salinas M, Rossel V. Rhabdomyolysis and acute renal failure after cocaine overdose: report of one case. Rev Med Chile. 2011 Apr;139(4):480–3.
79. Pimentel PV d S, Freitas HC, MDB L, RSA L, DMS B, Teixeira AC, et al. Rapidly progressive glomerulonephritis and acute kidney injury associated with cocaine use – case report. Braz J Nephrol. 2021;43(2):283–7.

80. Lorini Franciscatto I, Scherer Seibert B, Dries SS, Linden R, Ziulkoski AL, Perassolo MS. Evaluation of oxidative stress and its association with drug therapy in inpatients treated for cocaine dependence. Drug Chem Toxicol. 2023:1–9.
81. Magro MC d S, Vattimo M d FF. Avaliação da função renal: creatinina e outros biomarcadores. Rev Bras Ter Intensiva. 2007;19(2):182–5.
82. Milroy CM, Parai JL. The histopathology of drugs of abuse. Histopathology. 2011;59(4):579–93.
83. Adlakha A, Lobl J. A crack addict with extremely high creatine kinase levels. Hosp Pract. 1993;28(6):133–6.
84. M García-Rostán y Pérez G, Bragado FG, MPuras Gi A. Pulmonary hemorrhage and antiglomerular basement membrane antibody-mediated glomerulonephritis after exposure to smoked cocaine (crack): a case report and review of the literature. Pathol Int. 1997;47(10):692–7.
85. Bicca C, Ramos F, Campos V, Assis F, Pulchinelli A Jr, Lermnen N Jr, et al. Abuso e Dependência dos Opioides e Opiáceos. Associação Médica Brasileira: Projeto Diretrizes; 2012.
86. Coco TJ, Klasner AE. Drug-induced rhabdomyolysis. Curr Opin Pediatr. 2004 Apr;16(2):206–10.
87. O'Connor G, McMahon G. Complications of heroin abuse. Eur J Emerg Med. 2008;15(2):104–6.
88. Ferreira Abreu P, Kirsztajn GM, Fabiano De Franco M, Pereira AB. Revisão: Glomerulosclerose segmentar e focal colapsante Collapsing focal segmental glomerulosclerosis, vol. 24. J Bras Nefrol; 2002.
89. Amaral RA d, Malbergier A, Andrade AG d. Manejo do paciente com transtornos relacionados ao uso de substância psicoativa na emergência psiquiátrica. Rev Bras Psiquiatr. 2010;32(suppl 2):S104–11.
90. Scott RB, Reddy KS, Husain K, Schlorff EC, Rybak LP, Somani SM. Dose response of ethanol on antioxidant defense system of liver, lung, and kidney in rat. Pathophysiology. 2000;7(1):25–32.
91. Yuan HC, Yu QT, Bai H, Xu HZ, Gu P, Chen LY. Alcohol intake and the risk of chronic kidney disease: results from a systematic review and dose–response meta-analysis. Eur J Clin Nutr. 2021;75(11):1555–67.
92. Surma S, Więcek A. Alcohol and health. Does regular drinking of small dose of alcohol really good for your health? Arch Med Sci Atheroscler Dis. 2022;7(1):49–59.
93. Oliveira AB d S, Pereira ACP, Figueiredo BQ d, Ferreira C d C. Efeitos deletérios do uso crônico de álcool sobre a função orgânica humana: uma revisão integrativa de literatura. Res Soc Dev. 2022;11(9):e15411931873.
94. Jordão A Jr, Chiarello P, Bernardes M, Vannuchi H. Peroxidação lipídica e etanol: papel da glutationa reduzida e da vitamina E. Medicina (B Aires). 1998;31:434–49.

6 Nephropathy Associated with the Use of Herbal Medicine

Rolando Claure-Del Granado,
Jonathan S. Chávez-Íñiguez,
and Maria de Los Ángeles Espinosa-Cuevas

6.1 Introduction

The use of medicinal plants and herbal preparations is an ancient practice that remains common in many regions of the world, particularly in tropical areas such as Brazil. However, indiscriminate use of these remedies can lead to serious kidney complications. Herb-induced nephropathy has emerged as a major cause of kidney damage, especially in vulnerable populations with limited access to modern healthcare. This chapter discusses the mechanisms of kidney damage associated with the use of medicinal plants, the particular risks for patients with pre-existing kidney disease, and the importance of medical awareness in preventing such cases.

R. Claure-Del Granado (✉)
Division of Nephrology, Hospital Obrero No 2 - Caja Nacional de Salud, Cochabamba, Bolivia

IIBISMED, Facultad de Medicina Universidad Mayor de San Simón, Cochabamba, Bolivia

J. S. Chávez-Íñiguez
Servicio de Nefrología, Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Jalisco, Mexico

Universidad de Guadalajara Centro de Ciencias de la Salud, Guadalajara, Jalisco, Mexico

M. de Los Ángeles Espinosa-Cuevas
Departamento de Nefrología y Metabolismo Mineral, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, Mexico

6.2 Mechanism of Kidney Damage from Herbal Medicine

Herbal drugs or nutraceuticals can cause various side effects, including adverse reactions such as acute kidney injury (AKI) [1]. The clinical manifestations of AKI are varied, but the most common reports are acute interstitial nephritis and acute tubular necrosis, as well as electrolyte disturbances such as hypokalemia and Fanconi syndrome.

The mechanisms involved in herbal-induced AKI are multiple and complex, and our understanding is limited, making it difficult to identify and manage them properly. Some compounds with nephrotoxic potential in herbal medicine, such as methyl salicylate, saponin, latex, alkaloids, or licorice, have been identified as being able to induce acute interstitial nephritis through the infiltration of inflammatory cells in the peritubular capillaries, resulting in fibrosis and tissue atrophy. Acute tubular necrosis is caused by ischemia-reperfusion-induced damage and direct toxicity on renal tubule cells.

When analyzing the renal segments affected by herbal compounds, it has been observed that *Hypoxis hemerocallidea* impacts the glomerular filtration rate, while compounds such as *Ginkgo biloba* extract affect solute secretion in the renal tubule. Regarding solute reabsorption in this same segment, effects of plants such as

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_6

Arctostaphylos uva-ursi, *Trigonella foenum-graecum*, and *Crataegus orientalis* have been described.

Another physiological aspect altered by the consumption of herbs is the activity of some renal enzymes, such as CYP2B6, CYP3A5, UGT1A6, UGT1A9, and UGT2B7, which can be induced or inhibited by different herbs, altering the action of other drugs and renal physiological processes.

Additionally, renal damage can be due to adulterants in herbal products, a common practice that often goes unnoticed. Among the most reported compounds that have been associated with kidney damage are *Mucuna pruriens*, *Mucuna utilis*, *Aristolochia fangchi*, and chemicals such as paraphenylenediamine [2, 3].

6.3 Use of Herbal Medicine in the Treatment of Kidney Diseases

Throughout history, various plants have been used to treat kidney diseases, some of which have limited evidence but are supported by biological reasoning (Table 6.1).

Table 6.1 Herbs that are commonly used in the treatment of various kidney diseases

Product	Effect
Desmodium canadense	Antioxidant and nephroprotector
Tinospora cordifolia	Kidney injury reduction
Aerva lanata	Antioxidant
Gingko biloba	Reduction in lipid, urea, and creatinine peroxidation
Terminalia chebula	Reduction in urea and creatinine
Crataeva nurvala	Antioxidant
Bauhinia variegata	Reduction in urea and creatinine
Brassica nigra y rapa	Reduction in urea and creatinine and tissue injury
Bryophyllum calycinum	Nephroprotector
Carum carvi	Nephroprotector
Rubia cordifolia	Antioxidant
Cassia occidentalis	Antioxidant
Citrullus colocynthis	Antioxidant
Punica granatum Linn.	Nephroprotector
Allium sativum	Kidney function improvement
Vitis vinifera (resveratrol)	Tubular function improvement
Tamarindus indica	Antioxidant
Silybum marianum	Reduction in urea and creatinine
Ficus religiosa	Reduction in urea and creatinine

A well-known example is resveratrol, which may act as a nephroprotector by increasing nitric oxide, promoting vasodilation, and reducing oxidative stress and inflammation [4]. Other herbs with potential benefit, but with limited evidence, include ginger, ginseng, *Radix bupleuri*, *Camellia sinensis*, *Aerva javanica*, *Cassia auriculata*, *Emblica officinalis*, *Ficus religiosa*, *Solanum nigrum*, *Withania somnifera*, *Spina gleditsiae*, and turmeric [4].

Traditional Chinese medicine has also been shown to reduce the risk of kidney deterioration in people with chronic kidney disease (CKD). In a retrospective study of 24,971 CKD patients, 45% regularly used Chinese herbal medicine. After several analyses, a 59% reduction in the risk of developing end-stage kidney disease was observed [5]. A study in Hong Kong, with 38 patients with diabetes and CKD, showed that Chinese medicine users had a lower loss of glomerular filtration rate (eGFR), with adverse effects comparable to non-users [6].

Formulations such as rehmannia-6 (Liu-wei-di-huang-wan) appear to attenuate inflammatory and fibrotic pathways mediated by TNF [7], which may offer a new therapeutic avenue in the treatment of diabetic nephropathy, different from SGLT2 or renin-angiotensin-aldosterone system inhibitors [8].

The strongest evidence comes from the SCHEMATIC clinical trial, where the efficacy of rehmannia-6 on renal function in patients with diabetes and CKD was evaluated, demonstrating a lower loss of eGFR (2.7 mL/min per 1.73 m^2/year) compared to the placebo group [9].

Finally, another retrospective study with 14,718 patients with CKD showed that consumption of Chinese herbs, such as *Salvia miltiorrhiza* and Ji-Sheng-Shen-Qi-Wan, was associated with a reduction in the risk of long-term mortality [10].

6.4 Acute Kidney Injury

The use of medicinal plants represents a major environmental cause of nephrotoxicity, contributing significantly to the incidence of acute kidney injury (AKI) in several regions of Africa, Asia, and Latin America. An estimated 18% of community-acquired AKI cases worldwide are associated with the use of these medicinal plants [11]. In southern Africa and parts of Asia, herbal remedies are the most common factor associated with community-acquired AKI. In Nigeria, up to 37% of AKI cases have been linked to the use of traditional herbal medicines [12]. The mechanisms by which these plants cause nephrotoxicity include direct damage to renal tubular cells, ischemia, pigmenturia, and acute allergic interstitial nephritis.

A number of medicinal plants have been associated with the development of AKI (Table 6.2). Among the most common are *Securidaca longepedunculata* (violet tree), which contains methyl salicylate and saponins; *Euphorbia matabelensis*, with toxic latex; *Crotalaria laburnifolia*, which has alkaloids toxic to the liver and kidneys; *Lepidium meyenii* (maca); *Tripterygium wilfordii* (Lei Gong Teng); *Glycyrrhiza glabra* (licorice); *Callipedis laureola* (impila); and *Cape aloe* (*Aloe ferox* or *Aloe vera*). Some of these plants and their possible mechanisms of nephrotoxicity are explored below.

Tripterygium wilfordii, used in traditional Chinese medicine for over 2000 years, is used to treat arthritis and acute inflammation, as well as autoimmune diseases such as rheumatoid arthritis, lupus, and minimal change disease. Adverse effects include gastrointestinal problems, infertility, and suppression of the immune system. In animal studies, daily administration of a compound derived from this plant for 16 days resulted in acute tubular necrosis in rats [13].

In Latin America, one of the most reported cases of AKI is linked to the use of *Uncaria tomentosa* (cat's claw), a woody plant native to

Table 6.2 Medicinal plants related to acute kidney injury (AKI) in Latin America, with emphasis on countries where cases have been reported, including Brazil

Product	Countries with reports	Reports in Brazil
Aristolochia spp. (*Aristolochia*)	Mexico, Brazil, Venezuela, Colombia	Yes. Common in the Amazon region
Anadenanthera colubrina (curupay)	Brazil, Argentina, Bolivia	Yes. Used in traditional medicine
Tecoma stans (tronadora)	Mexico, Brazil	Yes. Used as traditional treatment for diabetes
Peumus boldus (boldo)	Chile, Brazil, Peru	Yes. Generalized use in Brazil for digestive problems
Uncaria tomentosa (cat's claw)	Peru, Brazil, Bolivia	Yes. Used in Brazilian traditional medicine to treat inflammation
Chelidonium majus (celidonia)	Mexico, Brazil	Yes. Used in popular Brazilian medicine
Morinda citrifolia (noni)	Brazil, Mexico, Costa Rica, Nicaragua	Yes. Popular use in Brazil for diverse health problems
Phyllanthus niruri (stonebreaker)	Brazil, Peru, Colombia	Yes. Popular in Brazil for kidney stone treatment
Ruta graveolens (Ruta)	Brazil, Argentina, Paraguay, Mexico	Yes. Used in popular Brazilian medicine for gynecological problems
Tibouchina mutabilis (Quaresmeira)	Brazil	Yes. Used in popular medicine to treat infections and digestive problems
Salvia divinorum (Salvia)	Mexico, Brazil	Yes. Used in Brazil as hallucinogenic plant

the Amazon. In countries such as Peru, it is used to treat cirrhosis, gastritis, gonorrhea, genitourinary neoplasias, and rheumatism. It is believed that the oxindole alkaloids present in the root bark are responsible for its therapeutic effects, although other unidentified compounds may be involved. Cases of acute interstitial nephritis possibly due to an idiosyncratic allergic reaction have been documented following the use of this plant [14, 15].

In the Andean region, the plant known as yacon (*Smallanthus sonchifolius*), used primarily for its hypoglycemic properties to treat diabetes, has been shown to cause nephrotoxicity in animal studies when consumed for long periods [16]. On the other hand, Cape aloe has gained popularity in countries such as Bolivia for the treatment of various types of cancer, which has increased its consumption in various forms, from pure preparations to mixtures with water, increasing the reported cases of AKI related to its use. In South Africa, Cape aloe is one of the main causes of AKI [17].

Maca (*Lepidium meyenii*), widely used in traditional South American herbal medicine, is consumed for its energizing properties and as an aphrodisiac. In Bolivia, it is known as the "Andean Viagra." However, daily consumption of between 2 and 3.5 grams of maca for 1 to 3 months has caused adverse effects such as weight loss, nausea, abdominal pain, and vomiting [18].

Flavonoids, used in Europe to treat circulatory disorders, liver disease, and adverse effects of radiotherapy, can also induce AKI. In traditional Chinese medicine, extracts of *Taxus celebica*, containing the flavonoid sciadopitysin, are used for the treatment of diabetes mellitus [19]. Symptoms of flavonoid poisoning include fever, gastrointestinal upset, dark urine, and oliguric AKI, characterized by tubular necrosis and acute interstitial nephritis. Although the exact mechanism is not fully understood, direct toxicity accumulated in renal tubular cells is suspected.

Finally, mushrooms also represent an important source of nephrotoxicity, especially in cases of liver failure induced by the ingestion of poisonous species. Gastrointestinal symptoms usually appear soon after ingestion, but signs of AKI may take 1–3 weeks to manifest. In Europe and North America, mushrooms of the *Cortinarius* genus have been confused with edible varieties, leading to multiple poisonings. In 2011, 6818 exposures to *Cortinarius* were reported in the United States and associated territories, resulting in 2 deaths [20]. Most cases involved unidentified species, suggesting that exposure to *Cortinarius* might be more common than reported. In one case series, eight patients who consumed *Cortinarius orellanus* developed AKI, six in severe condition, and four of them required renal replacement therapy. The severity of AKI and its progression to chronic kidney disease (CKD) were directly correlated with the amount ingested [21].

6.5 Chronic Kidney Disease

Many common herbal supplements are not subject to rigorous quality controls to ensure their content and safety, which can be especially harmful for people with chronic kidney disease (CKD) [22]. Patients with pre-existing CKD are at risk of developing complications from the use of herbal medicines. For example, *Ginkgo biloba* can cause bleeding complications, glycyrrhizic acid (found in licorice) can cause hypertension and hypokalemia, and herbs such as alfalfa or noni juice (*Morinda citrifolia*) are associated with hyperkalemia. Other examples include star fruit (*Averrhoa carambola*), which causes encephalopathy, and cranberry juice, which is linked to nephrolithiasis [23].

Since the 1990s, cases of kidney disorders such as urothelial carcinoma and irreversible renal interstitial fibrosis have been reported in people who consumed preparations containing species of the genus *Aristolochia*. These adverse effects have generally been observed with doses exceeding 200 grams [24]. Chinese herbal preparations have gained popularity in the United States and Europe, and these solutions have frequently been associated with toxic effects. In some cases, such as in Belgium between 1990 and 1992, toxic exposures occurred when

Aristolochia fangchi was mistakenly used instead of *Stephania tetrandra* in herbal weight-loss supplements. Similarly, species such as *Aristolochia manshuriensis* were substituted with other plants, such as *Clematis armandii*, *C. montana*, or *Akebia quinata*, since all four share the same Chinese name, Mu Tong. Similar cases have been reported in France, Japan, the United Kingdom, and Taiwan [25].

In Belgium, weight-loss supplements containing *Aristolochia fangchi* were sold in pharmacies until cases of progressive renal interstitial fibrosis began to emerge. All patients had followed the same regimen and were diagnosed with this condition through renal biopsies. Many of these individuals experienced rapid deterioration of kidney function, necessitating dialysis. *Aristolochia fangchi* was found to contain aristolochic acids (AA), which were identified as the cause of the kidney damage. Follow-up studies revealed that more than 80 women were affected and more than half required a kidney transplant. A similar case occurred in Spain, where renal interstitial fibrosis, clinically similar to the Belgian cases, was linked to regular consumption of an infusion made from *Aristolochia pistolochia* [26].

In addition to AA-related cases, there are other renal syndromes caused by unadulterated herbs, usually resulting from abuse or ignorance of proper administration (Table 6.3). In many cases, the exact mechanisms of kidney damage caused by these substances are not fully studied. Since adverse event reports are voluntary and many come from isolated case studies, it is likely that most commonly used herbs are not nephrotoxic. However, chronic kidney disease has been described in association with the consumption of certain plants [23].

Table 6.3 Main renal syndromes and associated herbal medicine

Renal syndrome	Herbal medicine
Acute tubular injury	African medicine: *Securidaca longepedunculata*, *Euphorbia matabalensis*, *Crotalaria laburnifolia* Sri Lanka's medicine: *Crotalaria* spp., *Cassia auriculata*, *Holarrhena antidysenterica* Chinese herbs (contaminated with arsenic): Niu Huang Chieh Tu Pien Morocco: *Takaout Rournia* Sudan: adulterated henna with paraphenylenediamine and cantharidin
Acute interstitial nephritis	South America (Peru and Bolivia): cat's claw Africa: *Aloe ferox* China: *Taxus celebica*, Chinese herbs adulterated with aristolochic acids; *Aristolochia* spp., *Akebia* spp., Mu Tong, Boui, Mokutsu China: Jua Wey Guo Sao pills (mixed herbs without *Aristolochia*)
Chronic interstitial nephritis	Chinese herbs with aristolochic acids; *Aristolochia* spp., *Akebia* spp., Mu Tong, Boui, Mokutsu China: Pildoras Jua Wey Guo Sao
Proximal tubulopathy (Fanconi syndrome)	*Glycyrrhiza* spp. (mixed herbs for cough), Chinese tea, gancao, Boui-ougi-tou Chinese herbs contaminated with cadmium Chinese herbs with aristolochic acids; *Akebia* spp., Boui-ougi-tou, Mokutsu
Analgesic nephropathy	Corteza de sauce (*Salix* spp.) Chinese herbs adulterated with NSAIDs (indomethacin, diclofenac, mefenamic acid, phenylbutazone), pills with Chuifong Tuokuwan and Tung Shueh
Hypertension	*Glycyrrhiza* spp. (mixed herbs for cough), Chinese herbal tea, gancao, Boui-ougi-tou
Kidney stones	Herbal preparations with *Ephedra* (Ma Huang), supplements with *Ephedra*'s alkaloids Cranberry juice (oxalate)
Kidney allograft rejection	Immunosuppressive drugs' interactions with alterative medicines; San Juan herb Immunostimulants: alfalfa (*Medicago sativa*)
Urine retention	Niger: *Datura* spp. (Sobi-lobi) Chinese herbs: *Rhododendron molle*, *Rehmannia glutinosa*, *Carthamus tinctorius*, *Atropa belladonna*, *Hyoscyamus niger*, *Datura* spp.
Urinary tract carcinoma	Chinese herbs with *Aristolochia* spp.: "Belgium diet" to weight loss

To better understand the risk of developing de novo CKD or progression of existing CKD from herbal use, Espinosa et al. conducted a study to identify the most commonly consumed nephrotoxic herbal medicines by patients at risk for developing chronic kidney disease [27]. The study found that 79.2% of participants had consumed at least one nephrotoxic herb in the past 12 months, with women reporting higher use than men ($P < 0.001$). Patients from both low and high socioeconomic status consumed nephrotoxic herbal supplements. Among patients with diabetes mellitus, 90% reported using nephrotoxic herbs, while 83% of hypertensive patients did the same. Specific herbs consumed by diabetic patients included horsetail and noni (33.3%), wormwood (26.7%), alfalfa, and aloe vera (23.3%). In hypertensive patients, alfalfa was used in 53.4% of cases, followed by aloe vera (43.4%), horsetail (33.4%), wormwood (30.0%), and noni (26.7%). Notably, patients taking nephrotoxic medications such as NSAIDs also consumed herbal supplements, such as ginger (40%), aloe vera (33.3%), noni (23.4%), and wormwood and dandelion (23.3% each).

Interestingly, 60% of patients indicated that their use of herbs was based on recommendations from friends or relatives, while 28.3% were advised by herbalists or vendors in local markets. Furthermore, 82% of patients did not inform their physicians about their consumption of herbal supplements, as they believed that these products were safe due to their natural origin.

The National Kidney Foundation has issued the following recommendations for CKD patients considering the use of herbal supplements to prevent disease progression [28, 29]:

- Consult with your physician, nutritionist, or product manufacturer about safety, dosage, duration of use, interactions with prescription medications, etc.
- Use only standardized herbal extracts from reputable companies.
- Never take more than the recommended dose or use for longer than directed.
- Avoid using herbal remedies for serious illnesses.
- Do not use herbs if you are thinking about becoming pregnant.
- Remember that "natural" does not mean "safe," especially for CKD patients. Be cautious and ask questions before using any herbal product.
- What may be safe for healthy people may not be safe for someone with CKD and may in fact be dangerous. Therefore, extreme caution should be used when using these products.
- Herbal supplements are not regulated by the government, so it is not known exactly what they contain, making the purity, safety, and efficacy of these products uncertain.

6.6 Conclusions

The use of traditional medicinal plants remains prevalent due to cultural beliefs and limited access to conventional healthcare. However, the consumption of herbs such as *Aristolochia*, associated with aristolochic acids, has been linked to chronic interstitial nephropathy and urothelial carcinoma in various regions, including Brazil. Furthermore, the use of unregulated herbal preparations, often contaminated with heavy metals and other toxins, has led to an increase in cases of acute kidney injury and chronic kidney disease. The lack of rigorous studies on the toxicity of many of these plants underscores the urgent need to investigate their adverse renal effects and promote greater regulation of their use. In summary, herbal nephropathy represents a growing public health challenge in Latin America, especially in rural communities where traditional medicine prevails.

References

1. Sri Laasya TP, Thakur S, Poduri R, Joshi G. Current insights toward kidney injury: Decrypting the dual role and mechanism involved of herbal drugs in inducing kidney injury and its treatment. Curr Res Biotechnol. 2020;2:161–75.
2. Isnard Bagnis C, Deray G, Baumelou A, Le Quintrec M, Vanherweghem JL. Herbs and the kidney. Am J Kidney Dis. 2004;44(1):1–11.

3. Srirama R, Santhosh Kumar JU, Seethapathy GS, Newmaster SG, Ragupathy S, Ganeshaiah KN, et al. Species adulteration in the herbal trade: causes, consequences and mitigation. Drug Safe. 2017;40(8):651–61.
4. Yang Y, Song M, Liu Y, Liu H, Sun L, Peng Y, et al. Renoprotective approaches and strategies in acute kidney injury. Pharmacol Ther. 2016;163:58–73.
5. Lin MY, Chiu YW, Chang JS, Lin HL, Lee CT, Chiu GF, et al. Association of prescribed Chinese herbal medicine use with risk of end-stage renal disease in patients with chronic kidney disease. Kidney Int. 2015;88(6):1365–73.
6. Chan KW, Chow TY, Yu KY, Feng Y, Lao L, Bian Z, et al. Effectiveness of integrative Chinese–Western medicine for chronic kidney disease and diabetes: a retrospective cohort study. Am J Chin Med. 2022;50(2):371–88.
7. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol. 2008;4(11):682–90.
8. Chan KW, Yu KY, Yiu WH, Xue R, Lok SW, Li H, et al. Potential therapeutic targets of rehmannia formulations on diabetic nephropathy: A comparative network pharmacology analysis. Front Pharmacol. 2022;13:794139.
9. Chan KW, Kwong ASK, Tan KCB, Lui SL, Chan GCW, Ip TP, et al. Add-on Rehmannia-6-based Chinese medicine in Type 2 diabetes and CKD: a multicenter randomized controlled trial. Clin J Am Soc Nephrol. 2023;18(9):1163–74.
10. Huang KC, Su YC, Sun MF, Huang ST. Chinese herbal medicine improves the long-term survival rate of patients with chronic kidney disease in Taiwan: a nationwide retrospective population-based cohort study. Front Pharmacol. 2018;9:1117.
11. Luyckx VA, Steenkamp V, Stewart MJ. Acute renal failure associated with the use of traditional folk remedies in South Africa. Ren Fail. 2005;27(1):35–43.
12. Kadiri S, Ogunlesi A, Osinfade K, Akinkugbe OO. The causes and course of acute tubular necrosis in Nigerians. Afr J Med Med Sci. 1992;21(1):91–6.
13. Dan H, Peng RX, Ao Y, Liu YH. Segment-specific proximal tubule injury in *Tripterygium* glycosides intoxicated rats. J Biochem Mol Toxicol. 2008;22(6):422–8.
14. Valerio LG Jr, Gonzales GF. Toxicological aspects of the South American herbs cat's claw (Uncaria tomentosa) and Maca (Lepidium meyenii): a critical synopsis. Toxicol Rev. 2005;24(1):11–35.
15. Hilepo JN, Bellucci AG, Mossey RT. Acute renal failure caused by 'cat's claw' herbal remedy in a patient with systemic lupus erythematosus. Nephron. 1997;77(3):361.
16. de Oliveira RB, de Paula DA, Rocha BA, Franco JJ, Gobbo-Neto L, Uyemura SA, et al. Renal toxicity caused by oral use of medicinal plants: the yacon example. J Ethnopharmacol. 2011;133(2):434–41.
17. Mathew AJ, George J. Acute kidney injury in the tropics. Ann Saudi Med. 2011;31(5):451–6.
18. Hudson A, Lopez E, Almalki AJ, Roe AL, Calderon AI. A review of the toxicity of compounds found in herbal dietary supplements. Planta Med. 2018;84(9–10):613–26.
19. Colson CR, De Broe ME. Kidney injury from alternative medicines. Adv Chronic Kidney Dis. 2005;12(3):261–75.
20. Bronstein AC, Spyker DA, Cantilena LR Jr, Rumack BH, Dart RC. 2012 Annual report of the American association of poison control centers' national poison data system (NPDS): 30th annual report. Clin Toxicol (Phila). 2012;50(10):911–1164.
21. Grebe SO, Langenbeck M, Schaper A, Berndt S, Aresmouk D, Herget-Rosenthal S. Antioxidant treatment and outcome of Cortinarius orellanus poisoning: a case series. Ren Fail. 2013;35(10):1436–9.
22. Singh SK, Jha SK, Chaudhary A, Yadava RD, Rai SB. Quality control of herbal medicines by using spectroscopic techniques and multivariate statistical analysis. Pharm Biol. 2010;48(2):134–41.
23. Jha V. Herbal medicines and chronic kidney disease. Nephrology (Carlton). 2010;15(Suppl 2):10–7.
24. Asif M. A brief study of toxic effects of some medicinal herbs on kidney. Adv Biomed Res. 2012;1:44.
25. Luciano RL, Perazella MA. Aristolochic acid nephropathy: epidemiology, clinical presentation, and treatment. Drug Saf. 2015;38(1):55–64.
26. Pena JM, Borras M, Ramos J, Montoliu J. Rapidly progressive interstitial renal fibrosis due to a chronic intake of a herb (Aristolochia pistolochia) infusion. Nephrol Dial Transplant. 1996;11(7):1359–60.
27. Claure-Del Granado R, Espinosa-Cuevas M. Herbal nephropathy. Contrib Nephrol. 2021;199:143–54.
28. Rashrash M, Schommer JC, Brown LM. Prevalence and predictors of herbal medicine use among adults in the United States. J Patient Exp. 2017;4(3):108–13.
29. Vanherweghem J-L. Nephropathy and herbal medicine. Am J Kidney Dis. 2000;35(2):330–2.

7 Haff Disease

Karla Cristina Petruccelli Israel, Mathias Alberto Schramm, Tatyana Costa Amorim Ramos, Michael do Nascimento Correia, Felipe Costa Neves, and Polianna Lemos Moura Moreira Albuquerque

7.1 Introduction

Haff disease, also known as "paroxysmal foodborne toxic rhabdomyolysis," is characterized by outbreaks of poisoning associated with the ingestion of freshwater or saltwater fish and crustaceans, which, due to lesion processes that are not yet fully understood, leads to the destruction of myocytes and potential acute kidney injury (AKI) [1]. Although its first descriptions date back a century, many questions regarding Haff disease still remain unanswered, demanding further and more intensive studies on the subject. Based on the World Health Organization's concept of One Health [2], which considers a multisectoral, transdisciplinary, transcultural, integrated, and unifying global approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems, Haff disease represents a condition that directly affects these relationships. Thus, given its characteristics, this entity has the potential to easily induce social panic [3], demanding further and more intensive studies on the subject.

K. C. Petruccelli Israel (✉) · M. A. Schramm
T. C. A. Ramos · M. do Nascimento Correia
Universidade Federal do Amazonas,
Manaus, Amazonas, Brazil
e-mail: mathias.schramm@ifsc.edu.br

F. C. Neves
Escola Bahiana de Medicina e Saúde Pública,
Salvador, Bahia, Brazil

P. L. M. M. Albuquerque
School of Medicine, Charles Darwin Universit,
Faculty of Health, Darwin, Australia

7.2 History and Epidemiology

The first records of paroxysmal foodborne toxic rhabdomyolysis in the literature date back to 1924, when outbreaks of "paralysis" and "black urinary events" were described in populations living on the shores of Lake Königsberg (now the Vistula Lagoon) in former East Prussia. The victims, mostly fishermen, developed symptoms hours after eating cooked fish—eel (*Anguilla anguilla*), pike (*Esox* spp.), or walleye (*Sander vitreus*)—and deaths were recorded [4, 5]. In addition to cases in humans, there were reports of fish and domestic and wild animal deaths, which led to the hypothesis of poisoning by substances present in the region, which ended up determining the name by which the disease is most widely known, since "Haff" is the German term for "lagoon." [4] In subsequent years, cases of the disease were recorded in other regions of Europe, notably in Sweden and Russia. In these countries, the fish species associated with the outbreaks were burbot (*Lota lota*), perch (*Perca fluviatilis*), and walleye, which are known to prey on other fish species. The first cases in the Americas occurred in 1984, in the USA, in Texas, and in California, associated with the ingestion of buffalo fish (*Ictiobus cyprinellus*).

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_7

The largest case series recorded by now is from China, including 1118 individuals who were diagnosed over a 16-year period. In the Chinese registry, most cases were associated with the consumption of crustaceans [4].

In Brazil, the first outbreak of Haff disease was recorded by Santos et al. [6] in the summer of 2008 in the city of Manaus, Amazonas, when 25 people were hospitalized with severe myalgia after consuming fish from the Amazon River—pacu (*Mylossoma* spp.) (Fig. 7.1), tambaqui (*Colossoma macropomum*) (Fig. 7.2), and pirapitinga (*Piaractus brachypomus*) (Fig. 7.3). The country recorded new cases again, this time in the state of Bahia between 2016 and 2017, associated with the consumption of saltwater fish of the species olho-de-boi (*Seriola* spp.) (Fig. 7.4) and badejo (*Mycteroperca* spp.) (Fig. 7.5). Between

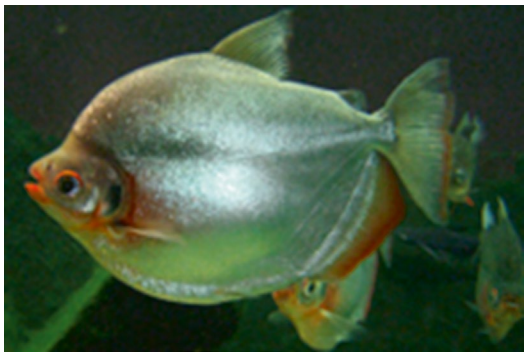


Fig. 7.1 Pacu (*Mylossoma* spp.). (Source: Wikipedia)

Fig. 7.2 Tambaqui (*Colossoma macropomum*). (Source: Wikipedia)

Fig. 7.3 Pirapitinga (*Piaractus brachypomus*). (Source: Wikipedia)

Fig. 7.4 Bull's eye fish (*Seriola* spp.). (Source: https://www.fiocruz.br/biosseguranca/Bis/infantil/olhodeboi.htm)

Fig. 7.5 Badejo (*Mycteroperca* spp.). (Source: Wikipedia)

2021 and 2022, the largest outbreak of Haff disease in the history of Brazil occurred, with 391 cases and 9 deaths recorded. The northern region of the country was the most affected in this outbreak (83.1%), with Amazonas being the state with the highest number of occurrences (179, 45.8%) [4].

In all records, there is a predominance of incidence among adults, most likely due to low fish consumption among children, with no gender predominance. The interval between fish consumption and the onset of symptoms varies from 1 to 48 hours, but on average, it is 6 to 8 hours. There are records of greater toxicity in the consumption of viscera, caviar, and fat from predatory fish, and it has been observed that symptoms appear after the consumption of cooked, fried, or baked fish, which suggests the existence of a heat-stable toxin. An interesting fact observed during the records of the 2021 and 2022 outbreak in the Amazon was that there was only an association of cases with the consumption of free-living fish as opposed to those raised in captivity, which suggests a strong environmental association with the incidence of rhabdomyolysis cases [4].

7.3 Etiological Hypotheses

Since the first reports of the so-called Haffkrankheit, [6, 7] different etiological hypotheses have been suggested and investigated [4]. Meyer [8] stated that no other book had described such symptoms and effects in humans; however, a similar disease was known in horses, which they called "paralytic hemoglobinuria" or "black urinary events." Dörbeck [9, 10] reported other hypotheses of the time, among them that the disease was related to the inhalation of toxic gases that rose from the water or from the bottom of the lake and that it was not arsenic hydride (AsH_3) poisoning, as some speculated, since the clinical symptoms were clearly distinct. In addition to the clinical and laboratory tests possible at the time, investigations into the causes of Haff disease involved tests such as spectroscopic examinations of blood and urine [8] and biological tests with animals [11–13] in addition to necropsies to verify anatomical and pathological changes in the tissues of affected animals and humans [14]. After many years of investigation, German researchers still had no answer as to the origin of the disease. They concluded that the hypothesis of bacterial or viral infection could be ruled out, assuming that the disease could be caused by a poison, possibly of an inorganic nature. Among the mentioned were resinous acids, hydrogen selenide, and selenium combined with tellurium and arsenic, present in iron ore. Another form of poisoning that was ruled out was botulinum toxin poisoning [15, 16].

Many other etiological hypotheses for Haff disease have been proposed, but it is still not possible to state precisely which agent or agents are responsible. Currently, the most widely accepted hypothesis is that the disease is caused by some phycotoxin or a toxic cocktail formed by several phycotoxins produced by microalgae [4].

It is possible that the first study to associate a phycotoxin with Haff disease was by Alcala et al. [1], who identified the presence of palytoxin in samples of the crab *Demania reynaudii*, which led to the death of a patient in the Philippines who consumed contaminated fish.

Palytoxin was described by Moore and Scheuer [17], produced by corals of the genus *Palythoa* sp. from the Hawaiian Islands. It is considered one of the most toxic non-protein toxins known, with different lethal doses (LD50) depending on the animal group and the form of administration of the toxin: 0.025 μg/kg (rabbit), 0.033 μg/kg (dog), 0.078 μg/kg (monkey), 0.089 μg/kg (rat), 0.11 μg/kg (guinea pig), and 0.45 μg/kg (mouse) [18, 19].

The European Union Health Authority [20] established the acute reference dose (ARfD) for humans as 0.2 μg/kg, suggesting a maximum permitted limit of 30 μg/kg in the meat of filter-feeding mollusks, such as mussels and oysters. In

addition to palytoxin, there are many other analogous molecules that make up the palytoxin group, including ostreocins, ovatoxins, and mascarenotoxins, produced by different aquatic organisms. The ostreocin-D molecule, for example, was described by Ukena et al. [21] as being produced by a marine dinoflagellate *Ostreopsis siamensis*. Ciminiello et al. [22] identified different ovatoxins produced by *Ostreopsis ovata* through high-resolution mass spectrometry. And a marine cyanobacterium of the genus *Trichodesmium* was identified as a producer of palytoxin and 42-hydroxy-palytoxin [23]. Recently, the first evidence of 42-hydroxy-palytoxin production by *Prorocentrum borbonicum*, a dinoflagellate found in the Caribbean Sea, which, in addition to producing borbotoxins, can produce palytoxin analogues, was presented [24].

In Brazil, strains of *Ostreopsis* cf. *ovata* have been identified in tropical and subtropical waters of different coastal regions such as Rio Grande do Norte, Bahia, Rio de Janeiro, São Paulo, and Paraná, as well as some oceanic islands [23], some of which produce palytoxin and ovatoxins [25–27].

Ramos and Vasconcelos [28] studied the biological and ecological effects of palytoxin and some analogues on different aquatic organisms, showing that different organisms from different trophic levels of the marine food chain are susceptible to being affected by these toxins, including products of commercial interest.

In addition to being a very potent toxin, palytoxin is known to cause rhabdomyolysis in humans [29] and to be associated with different poisoning events through fish consumption [30–32].

Diaz [33] presents and compares three poisonings known to produce rhabdomyolysis as an effect. These are cicutoxin poisoning, palytoxin poisoning, and Haff disease, all with very similar symptoms and effects. However, there is a consensus among many researchers that Haff disease is caused by some toxin or a cocktail of toxins similar to palytoxin.

Because it is a rare and infrequent disease, research is scarce and based on case studies, generally investigating the clinical and laboratory aspects associated with patients [33–36]. Some of these case studies have confirmed the relationship between Haff disease and fish consumption, even suggesting palytoxin as a probable cause of the disease [32, 37].

There are few studies that present results of investigations into the food consumed by patients with suspected Haff disease. One of the reasons is the impossibility of accessing the material, since in most cases there are no leftovers [4]. However, samples are occasionally collected and examined. Suzuki et al. [38], for example, analyzed samples of leftover parts of parrotfish consumed by patients who developed severe muscle pain. The chemical analyses were performed using liquid chromatography coupled to mass spectrometry, a highly sensitive and specific technique, but no signal corresponding to palytoxin was detected. This shows how difficult and complex the analysis of this type of molecules is, especially in biological matrices such as fish.

During the outbreak that occurred in northeastern Brazil between 2016 and 2017, fish samples were investigated by the FDA for the presence of biotoxins and heavy metals; however, none were found [39, 40]. Recently, in the outbreak that occurred in Bahia between 2020 and 2021, in natura samples and samples of leftovers from fish-based meals, including "olho-de-boi," were analyzed using LC-MS/MS methods. The results showed transition ions characteristic of isobaric palytoxin, and of some analogues, such as ovatoxin-a (OVTX-a), OVTX-b, and OVTX-d, mainly in the leftover meal samples, reinforcing the hypothesis that palytoxins are among the most likely toxic agents linked to Haff disease [41–43]. In marine environments, dinoflagellate microalgae and corals are the main organisms that produce biotoxins that accumulate in the food chain through bioaccumulation and biomagnification processes. In freshwater environments, cyanobacteria are the main group that produces biotoxins. However, their presence is not enough. Fish contamination usually occurs during harmful algal bloom (HAB) events [44] [45, 46].

7.4 Environmental Aspects

Between 2021 and 2023, Haff disease was recorded every year in the Amazon region, involving more than 350 patients who consumed fish such as pacu, tambaqui, and pirapitinga. The data show a spatial-temporal distribution of occurrences with a predominance between the cities of Manaus (Amazonas) and Santarém (Pará), especially between the months of June and November [47, 48], the period in which the Amazon River ebbs (Fig. 7.6).

According to the Epidemiological Bulletin No. 1/2024, from the Amazonas Health Surveillance Foundation [48], the state recorded 68 cases compatible with Haff disease between January and December 2023, distributed across 8 municipalities. The majority of cases (80.9%) occurred between the months of July and December, and two out of three (67.6%) were recorded in the municipality of Itacoatiara.

Considering that Haff disease is a poisoning caused by biotoxins produced by microalgae during bloom events and that they are transferred to fish while still in the aquatic environment, directly or indirectly, we can assume the hypothesis that the spatial-temporal distribution of Haff disease outbreaks in the Amazon region may be associated with environmental variations that influence the dynamics of this body of water. We can also consider that the frequency and distribution of poisoning cases are related to variations in river volumes and flows, in addition to flood and ebb cycles.

Leal et al. [49] conducted an epidemiological study on the relationship between sociodemographic and environmental parameters and the transmission of the hepatitis A virus in the state of Pará and observed that the transmission of the virus was positively associated with periods of intense precipitation. Kovats [50] reviewed the literature on the relationship between weather, climate, and human health, especially on climate variability and the El Niño-Southern Oscillation (ENSO), on environmental disasters, and on the occurrence and distribution of diseases such as malaria, dengue, cholera, and diarrheal poisoning in different regions of the world. Kovats states that there is good epidemiological evidence that ENSO is associated with an increased risk of certain diseases in specific geographic areas where it influences climate variations.

Studies show that the climatology of the Amazon is influenced not only by changes in the surface temperature of the equatorial Pacific Ocean but also by the surface temperature of the tropical Atlantic Ocean and that these variations affect the rainfall regime in the Amazon individually and in combination [51].

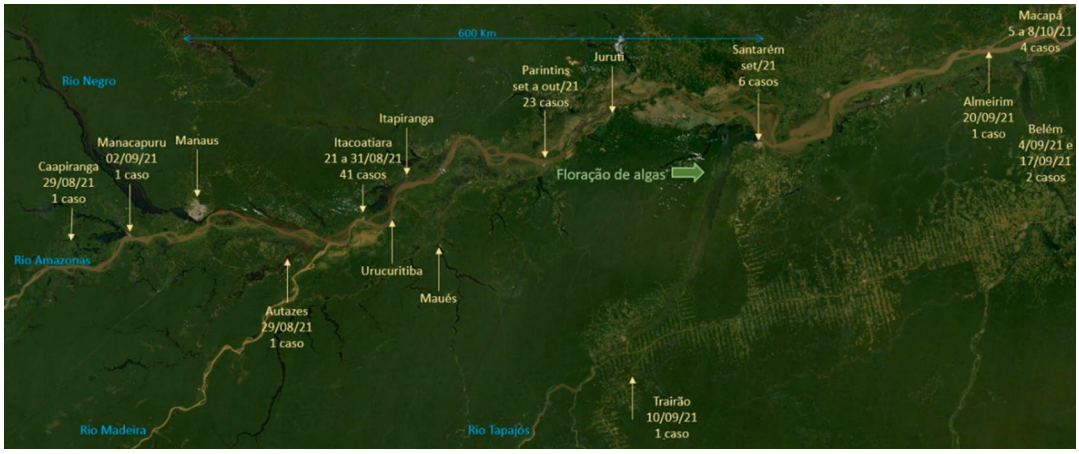


Fig. 7.6 Temporal distribution of Haff disease cases along the Amazon River. (Source: Prof. Dr. Mathias Alberto Schramm)

Assuming that the precipitation in the Amazon and, consequently, the volume of water in rivers are influenced by climatic and oceanographic phenomena associated with surface temperature anomalies in the Pacific and Atlantic Oceans, and these are influenced by global warming, we can expect that in the coming decades, we will see an increase in the impacts of climate variations on harmful algal blooms in the world and on the Amazon biome. Recent studies address these issues and warn of possible scenarios and impacts [52, 53]. Other hypotheses and variables should also be considered to support and explain the occurrence of Haff disease, both in the Amazon basin and on the Northeast Coast of Brazil, such as nutrient input, sources of pollution, mining, deforestation, dams, and urbanization, among others. However, the most important thing is that we have the best possible database and information to manage and minimize the impacts of food poisoning due to the consumption of contaminated fish.

7.5 Clinical and Laboratory Aspects

The symptom most commonly associated with Haff disease is myalgia, present in almost 100% of cases. Mainly affecting large muscle groups, the pain is of variable intensity and most frequently reported by patients in the cervical and lumbar regions. Chest pain is not uncommon, which requires the need for differential diagnosis with angina episodes, since the symptoms are often described as constrictive. Muscle weakness is also a common symptom and may even involve the respiratory muscles, resulting in dyspnea [4].

Gastrointestinal symptoms such as nausea, vomiting, and diarrhea may occur frequently, as well as abdominal pain, headache, and dizziness. The presence of dark urine, which popularly become synonymous of Haff disease ("black urine disease"), although quite common, was absent in up to 50% of cases in some series of records, a fact that may even suggest underdiagnosis in some regions. Other reported symptoms include paresthesia, pruritus, and xerostomia [4].

In laboratory terms, an increase in serum levels of creatine phosphokinase (CPK) to five times the normal value is a diagnostic parameter for Haff disease. In addition to CPK, other enzymes indicative of muscle injury, such as myoglobin, aldolase, and TGO, are elevated in Haff disease. Important data for the differential diagnosis in cases of chest pain are the absence of elevation in serum troponin levels and the proportion of the MB fraction in relation to total CPK, which should not exceed 5%. The pattern of elevation of muscle enzymes should also be observed: myoglobin rises first and may be normalized before CPK reaches its peak, which occurs between 24 and 72 hours after the injury. It should also be noted that significant elevations in CPK are often not observed before 12 hours after the onset of the injury, which requires laboratory reevaluation after 8 to 12 hours, when the diagnostic suspicion is important. The intensity of rhabdomyolysis according to serum CPK levels is described as mild, when levels are between 1000 and 5000 U/L; moderate when they are between 5000 and 15,000 U/L; and severe when serum levels are above 15,000 U/L. There is controversy regarding the existence of a direct relationship between serum CPK levels and the risk of unfavorable evolution—particularly in association with AKI—since the major tubular toxin is in fact myoglobin. However, even in the face of this paradox, most guidelines for the management of rhabdomyolysis are guided by serum CPK levels [4].

As with other rhabdomyolysis cases, several electrolytic changes are observed. Myocyte damage results in elevated serum levels of potassium, phosphorus, and uric acid. Hypocalcemia is also observed due to the calcium shift and the formation of complexes with released phosphorus [54].

Urinalysis has limited diagnostic utility. Mild hematuria and proteinuria may be observed. The presence of myoglobin in urine may be mistaken for hematuria by urinalysis test strips, resulting in a false-positive result. For a long time, positivity for heme in urine with the absence of red blood cells was considered essential for the diagnosis of rhabdomyolysis. However, this finding is only observed in 35% of patients with some degree of muscle damage [4].

7.6 Kidney Involvement in Haff Disease

As in other cases of toxic rhabdomyolysis, the main and most common kidney dysfunction observed in Haff disease is AKI. The mechanism by which the process develops is multifactorial, involving hypovolemia, metabolic acidosis, and tubular injury. Hypovolemia may result from losses associated with vomiting and diarrhea. Muscle injury per se causes fluid sequestration to the extracellular space, determining depletion of intravascular volume that activates the renin-angiotensin-aldosterone system, reducing renal plasma flow. There is an increase in vasoconstrictor agents such as endothelin-1, thromboxane A2, tumor necrosis factor α, and isoprostanes, in addition to a reduction in the vasodilatory effect of nitric oxide, attributed to the presence of myoglobin in the renal microcirculation. Myoglobin also exerts a direct cytotoxic effect on the nephron through the mechanism of cell membrane damage by lipid peroxidation, and the formation of oxygen free radicals after its degradation also produces tubular damage and leukocyte-mediated inflammation. The association with metabolic acidosis favors the formation of casts by interaction with the Tamm-Horsfall protein and the consequent tubular obstruction, notably in the distal convoluted tubules. Direct toxic damage mainly affects the proximal convoluted tubules [4]. The progression to severe renal injury and the need for renal replacement therapy in Haff disease are quite variable. Wu et al. [55] recorded an incidence of renal dysfunction of around 6.25% in a series of patients admitted to a single center in Beijing for rhabdomyolysis associated with the consumption of crustaceans. During the outbreak that occurred in the state of Bahia between 2016 and 2021, Cardoso et al. [41] reported an incidence of severe AKI of 7%, including the need for renal replacement therapy.

A very useful instrument in the prognostic assessment and in determining clinical approaches in cases of rhabdomyolysis is the severity score described and validated by McMahon [56] (Table 7.1). By assigning scores to clinical and laboratory data in cases of rhabdomyolysis, the score has a sensitivity of 86% and a specificity of 68% in predicting the need for RRT. Scores higher than 6 are associated with higher mortality and the need for RRT, thus suggesting a more intensive approach. We recommend using the adapted McMahon score, since the original score includes the cause of rhabdomyolysis as a variable for scoring, in which 0 points are attributed to toxic (e.g., statins) and inflammatory (myositis) rhabdomyolysis and 3 points to traumatic forms (crushing or post-cardiorespiratory arrest). Since Haff disease is a rhabdomyolysis of presumably toxic origin, we chose to assign 0 points to all patients.

Table 7.1 Escore de McMahon [56]

Variable	Values	Points
Age, years	<50	0
	51–70	1.5
	71–80	2.5
	>80	3
Gender	Male	0
	Female	1
Creatinine at admission	<1.4 mg/dL	0
	1.4–2.2 mg/dL	1.5
	>2.2 mg/dL	3
Calcium initial <7.5 mg/dL	No	0
	Yes	2
Cause of rhabdomyolysis	Convulsion, myositis, statin, exercise	0
	Other causes (trauma, burns, post-CPA[a])	3
Serum phosphate initial	<4.0 mg/dL	0
	>4.0–5.4 mg/dL	1.5
	>5.4 mg/dL	3
CPK >40,000 U/L	Yes	2
	No	0
Bicarbonate initial <19 mEq/L	Yes	2
	No	0

[a]*CPA* cardiopulmonary arrest; *CPK* creatine kinase

7.7 Clinical Management

There is no specific therapy for Haff disease. Therefore, once the diagnosis of Haff disease has been suspected based on a typical history and

after a thorough anamnesis, additional tests should be performed for early diagnosis and staging of rhabdomyolysis. In addition to instituting standard clinical stabilization measures and appropriate monitoring of hydroelectrolytic and acid-base disorders, the approach should include two basic laboratory parameters: serum CPK level and the McMahon score [56]. It is important to note that rhabdomyolysis is the central condition in the pathophysiology of Haff disease. Patients with mild rhabdomyolysis (between 1000 U/L and 5000 U/L of CPK) rarely require hospital admission and fluid resuscitation. However, if these patients have a McMahon score of 6 or higher, the procedure requires prompt fluid replacement. Patients with moderate and severe rhabdomyolysis should always be admitted and prescribed vigorous hydration, with volumes of 1500–2000 mL of crystalloid, which can be Ringer's lactate (when there is no acidosis) or bicarbonate solution, with strict monitoring of urinary volume. Hydration should only be suspended in cases of oliguria or signs of hypervolemia. In cases where bicarbonate solution is used, if the serum bicarbonate level exceeds 24 mEq/L, the solution should be replaced by Ringer's lactate. There is no consensus on the best solution to be used for volume resuscitation in rhabdomyolysis, including that associated with Haff disease. The Danish Society of Intensive Care guidelines on rhabdomyolysis [57] did not present any recommendations on the subject. We recommend adopting the protocol recommended by Cho et al. [58], which uses Ringer's lactate at a rate of 120 mL/h of infusion, reserving the bicarbonate solution for cases of metabolic acidosis. The use of mannitol or diuretics to prevent acute kidney injury caused by rhabdomyolysis, although widespread, is not supported by scientific evidence [59]. Concomitant electrolyte changes should be corrected promptly, except for hypocalcemia, due to the risk of worsening muscle damage due to the precipitation of calcium phosphate salts, in addition to the risk of rebound hypercalcemia. If preventive measures are unsuccessful, the indications for renal replacement therapy in Haff disease follow the guidelines recommended for other etiologies of acute kidney injury [4].

7.8 Conclusion

The number of reports of Haff disease has increased significantly since the beginning of the twenty-first century, although the entity should still be considered a rare disease. It is very likely that the disease is underdiagnosed, mainly because the symptoms are common to several other pathologies and there is often no detailed analysis of the epidemiological history of individuals treated in emergency units. The way in which the disease is popularly known ("black urine disease") also contributes to this underdiagnosis, since the brown coloration of the urine is only observed in approximately 40% of individuals with rhabdomyolysis, which may lead professionals to not measure CPK or investigate a history of fish consumption in patients with complaints of myalgia.

There is still much to be clarified about paroxysmal food-induced toxic rhabdomyolysis. What is the real toxin involved in the process? What is the true association of environmental changes, particularly climate changes, with the increased incidence of outbreaks? Is there a specific biological marker for diagnosing or determining the development of the syndrome? Why are there different responses to the same degree of exposure even in family clusters? These questions require answers that will only be obtained through interdisciplinary and multicenter efforts over the next few years. Such answers are urgently needed, especially given the potential economic, human, and social risk that outbreaks of Haff disease pose to populations exposed to them.

7.9 Take-Home Message

- Haff disease is associated with fish consumption, and its cause is not completely clear (whether it is a toxin or if environmental factors play a key role).
- It is not recommended to prohibit fish consumption, even in areas where cases have been reported. However, health surveillance services must be attentive to controlling water quality and possible environmental contaminants.

- Disease management is support, and there is no specific treatment.
- Hydration and supportive therapy are the basis of treatment, with dialysis indicated in specific cases of severe acute kidney injury.

References

1. Silva Junior FMR, Santos M. Haff's disease in Brazil - the need for scientific follow-up and case notification. Lancet Reg Health Am. 2021;5:100100.
2. World Health Organization. One Health. Available at: https://www.who.int/health-topics/one-health#tab=tab_1. Accessed 12 Sept 2024.
3. Pei P, Li XY, Lu SS, Liu Z, Wang R, Lu XC, Lu K. The emergence, epidemiology, and etiology of Haff disease. Biomed Environ Sci. 2019;32(10):769–78.
4. Aguiar GRF, Silva RCM, Pelli KCS, Oliveira MN, Brito GAU, Albuquerque PLMM, Daher EF, Silva Junior GB. Haff disease: overview and clinical features. Rev Inst Med Trop São Paulo. 2024;66:e52.
5. Lentz O. Über die Haffkrankheit [About Haff disease]. Med Klin. 1925;1:4–8.
6. Santos MC, Bernardino CA, Pinto RC, Aguiar GP, Lescano AG, Santos JHA, et al. Outbreak of Half disease in the Brazilian Amazon. Rev Panam Salud Publica. 2009;26(5):469–70.
7. Lawetzky. Die Haffkrankheit. Dtsch Med Wochenschr. 1924;50(42):1444.
8. Meyer S. Haffkrankheit und paralytische hämoglobinurie der pferde—identische krankheitszustände. Klin Wochenschr. 1924;48:2189–90.
9. Dörbeck F. Zur ätiologie der Haffkrankheit. Klin Wochenschr. 1926;18:799.
10. Lewin L. Untersuchungen an Hafffishern mit Haffkrankheit. Dtsch Med Wochenschr. 1925;51(4):133–4.
11. Joachimoglu G, Spinner JR. Zusammenfassung von Studienergebnissen (am Krankenbett und im Laboratorium). Dtsch Med Wochenschr. 1925;51:1483.
12. Fortner J. Tierversuche zur Aetiologie der Haffkrankheit. Dtsch Med Wochenschr. 1928;54(34):1414–5.
13. Assmann H, Bielenstein H, Habs H, Jeddeloh B. Befunde am Rückenmark bei der sogenannten "Haffkrankheit" der Katzen. Deutsche Medizinische Wochenschrift, Jahrgang. 1933;59(10):367–8.
14. Bürgers B, Bachmann A, Hettche F. Experimentelle Untersuchungen über die Ursache der Haffkrankheit. Dtsch Med Wochenschr. 1933;59(2):53–4.
15. Berlin R. Haff disease in Sweden. Acta Med Scand. 1948;129(6):560–72.
16. Alcala AC, Alcala LC, Garth JS, Yasumura D, Yasumoto T. Human fatality due to ingestion of the crab *Demania reynaudii* that contained a palytoxin-like toxin. Toxicon. 1988;26(1):105–7.
17. Moore RE, Scheuer PJ. Palytoxin: a new marine toxin from a coelenterate. Science. 1971;172(3982):495–8.
18. Wiles JS, Vick JA, Christensen MK. Toxicological evaluation of palytoxin in several animal species. Toxicon. 1974;12(4):427–33.
19. Vick JA, Wiles J. Pharmacological and toxicological studies of palytoxin. In: Hall S, Strichartz G, International Union of Pure and Applied Chemistry (Ab 1951. Marine toxins: origin, structure, and molecular pharmacology: developed from a symposium held in Woods Hole, Massachusetts, under auspices of the International Union of Pure and Applied Chemistry, and sponsored through an interagency agreement between the U.S. Army Medical Research Institute of Infectious Diseases and the Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration. Washington, DC: American Chemical Society; 1990. Chapter 19, p. 241–54.
20. Scientific Opinion on marine biotoxins in shellfish - Palytoxin group. EFSA J. 2009;7(12):1393.
21. Ukena T, Satake M, Usami M, Oshima Y, Naoki H, Fujita T, et al. Structure elucidation of Ostreocin D, a Palytoxin analog isolated from the dinoflagellate *Ostreopsis siamensis*. Biosci Biotechnol Biochem. 2001;65(11):2585–8.
22. Ciminiello P, Dell'Aversano C, Iacovo ED, Fattorusso E, Forino M, Grauso L, et al. Complex palytoxin-like profile of *Ostreopsis ovata*. Identification of four new ovatoxins by high-resolution liquid chromatography/mass spectrometry. Rapid Commun Mass Spectrom. 2010;24(18):2735–44.
23. Kerbrat AS, Amzil Z, Pawlowiez R, Golubic S, Sibat M, Darius HT, et al. First evidence of palytoxin and 42-hydroxy-palytoxin in the marine cyanobacterium *Trichodesmium*. Mar Drugs. 2011;9(4):543–60.
24. Arteaga-Sogamoso E, Riobó P, Rodríguez F, Mancera-Pineda JE, Franco-Angulo J. First record of the dinoflagellate *Prorocentrum borbonicum* in the continental coast of Colombian Caribbean: a new 42 hydroxi-palytoxin producer. Front Mar Sci. 2022;9:1–15.
25. Nascimento S, Neves R, De'Carli G, Borsato G, da Silva R, Melo G, et al. *Ostreopsis* cf. *ovata* (Dinophyceae) molecular phylogeny, morphology, and detection of Ovatoxins in strains and field samples from Brazil. Toxins. 2020;12(2):70.
26. Nascimento SM, Corrêa EV, Menezes M, Varela D, Paredes J, Morris S. Growth and toxin profile of *Ostreopsis* cf. *ovata* (Dinophyta) from Rio de Janeiro, Brazil. Harmful Algae. 2012;13:1–9.
27. Tibiriçá CEJA, Leite IP, Batista TVV, Fernandes LF, Chomérat N, Herve F, et al. *Ostreopsis* cf. *ovata* Bloom in Currais, Brazil: Phylogeny, toxin profile and contamination of Mussels and Marine Plastic Litter. Toxins. 2019;11(8):446.
28. Ramos V, Vasconcelos V. Palytoxin and analogs: biological and ecological effects. Mar Drugs. 2010;8(7):2021–37.
29. Okano H, Masuoka H, Kamei S, Seko T, Koyabu S, Tsuneoka K, et al. Rhabdomyolysis and myocar-

dial damage induced by Palytoxin, a toxin of blue Humphead parrotfish. Intern Med. 1998;37(3):330–3.
30. Onuma Y, Satake M, Ukena T, Roux J, Chanteau S, Rasolofonirina N, et al. Identification of putative palytoxin as the cause of clupeotoxism. Toxicon. 1999;37(1):55–65.
31. Yoshimine K, Orita S, Okada S, Sonoda K. Two cases of parrotfish poisoning with rhabdomyolysis. Nippon Naika Gakkai Zasshi. 2001;90(7):1339–41.
32. Taniyama S, Mahmud Y, Terada M, Takatani T, Arakawa O, Noguchi T. Occurrence of a food poisoning incident by palytoxin from a serranid Epinephelus sp. in Japan. J Nat Toxins. 2002;11(4):277–82.
33. Diaz JH. Rhabdomyolysis after cooked seafood consumption (Haff Disease) in the United States vs China. Ochsner J. 2015;15(2):170–5.
34. Krishna N, Wood J. It looked like a myocardial infraction after eating crawfish. Ever heard of Haff disease? Louisiana Morbidity Report. 2001;12(3):1–8.
35. Langley RL, Bobbitt WH. Haff disease after eating Salmon. South Med J. 2007;100(11):1147–50.
36. Paul V, Shamah S, Garankina O, Wolf L, Shia LY. Rhabdomyolysis after fish consumption: Haff's disease. QJM. 2013;107(1):67–8.
37. Taniyama S. The occurrence of palytoxin-like poisoning and ciguatera in parts of the main land of Japan. Nippon Suisan Gakkaishi. 2008;74:917–8.
38. Suzuki T, Watanabe R, Matsushima R, Ishihara K, Uchida H, Kikutsugi S, et al. LC-MS/MS analysis of palytoxin analogues in blue humphead parrotfish Scarus ovifrons causing human poisoning in Japan. Food Addit Contam Part A. 2013;30(8):1358–64.
39. Bandeira AC, Campos GS, Ribeiro GS, Cardoso CW, Bastos CJ, Pessoa TL, et al. Clinical and laboratory evidence of Haff disease - case series from an outbreak in Salvador, Brazil, December 2016 to April 2017. Euro Surveill. 2017;22(24):30552.
40. Almeida LKR, Gushken F, Abregu-Diaz DR, Muniz R, Degani-Costa LH. Rhabdomyolysis following fish consumption: a contained outbreak of Haff Disease in São Paulo. Braz J Infect Dis. 2019;23(4):278–80.
41. Cardoso CW, Oliveira e Silva MM, Bandeira AC, Silva RB, Prates APPB, Soares ES, et al. Haff disease in Salvador, Brazil, 2016-2021: attack rate and detection of toxin in fish samples collected during outbreaks and disease surveillance. Lancet Reg Health Am. 2021;5:100092.
42. Pierezan MD, Zanetti VC, Maran EM, Kleemann C, Hoff R, Verruck S. Investigando a etiologia da Doença de Haff: análise exploratória de amostras de peixe associadas ao surto ocorrido em novembro e dezembro de 2020 nos estados de Pernambuco e Bahia, Brasil. 1° Congresso de Segurança e Qualidade dos Alimentos [Internet]. 2022; 1(1). Available from: https://publicacoes.softaliza.com.br/csqa/article/view/3399/2614.
43. Pierezan MD, Zanetti VC, Maran EM, Kleemann C, Hoff R, Verruck S. Doença de Haff no Brasil: uma preocupação emergente e seu impacto sobre a cadeia produtiva de pescado nas regiões norte e nordeste. 1° Congresso de Segurança e Qualidade dos Alimentos [Internet]. 2022; 1(1). Available from: https://publicacoes.softaliza.com.br/csqa/article/view/3402/2616.
44. Hallegraeff GM, Anderson DM, Cembella AD, Enevoldsen HO. Manual on harmful marine microalgae. Paris: Unesco Publishing; 2004.
45. Lassus P, Chaumérat N, Hess P, Nézan E. Toxic and harmful microalgae of the World Ocean. [Internet] aquadocsorg. 2015. Available from: https://aquadocs.org/handle/1834/42206.
46. Garita-Alvarado CA, Bojorge-Garcia MG, Uriza EAC. Cyanotoxins bioaccumulation in freshwater ecosystems in Latin America: a review. Hidrobiologica. 2023;33(3):353–65.
47. Brasil. Ministério da Saúde. Boletim Epidemiológico, n 9, v 54. Brasília. Jun. 2023.
48. Brasil, Amazonas. Secretaria de Estado e Saúde. Doença de Haff: Boletim Epidemiológico. Ano 3. Jan. 2024.
49. Leal PR, José R, Kampel M. Associations between environmental and sociodemographic data and hepatitis-a transmission in Pará State (Brazil). Geohealth. 2021;5(5):e2020GH000327.
50. Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Niño and health. Lancet. 2003;362(9394):1481–9.
51. Souza SAS, Querino CAS, Querino JKAS, Martins PAS, Vaz MAB. Variabilidade da precipitação na mesorregião sul do Amazonas em decorrência de eventos de El Niño. RA'EGA, Curitiba, PR. 2022;54:23–36.
52. Hallegraeff GM, Anderson DM, Belin C, Bottein MYD, Bresnan E, Chinain M, et al. Perceived global increase in algal blooms is attributable to intensified monitoring and emerging bloom impacts. Commun Earth Environ. 2021;2:117.
53. Flores BM, Montoya E, Sakschewski B, Nascimento N, Staal A, Betts RA, et al. Critical transitions in the Amazon forest system. Nature. 2024;626(7999):555–64.
54. Nance JR, Mammen AL. Diagnostic evaluation of rhabdomyolysis. Muscle Nerve. 2015;51(6):793–810.
55. Wu CJ, Zhou HJ, Gu W. Clinical characteristics of patients with Haff disease after eating crayfish. World J Emerg Med. 2019;10(3):156–9.
56. McMahon GM, Zeng X, Waikar SS. A risk prediction score for kidney failure or mortality in rhabdomyolysis. JAMA Intern Med. 2013;173(19):1821–8.
57. Michelsen J, Cordtz J, Liboriussen L, Behzadi MT, Ibsen M, Damholt MB, et al. Prevention of rhabdomyolysis-induced acute kidney injury—a DASAIM/DSIT clinical practice guideline. Acta Anaesthesiol Scand. 2019;63(5):576–86.
58. Cho YS, Lim H, Kim SH. Comparison of lactated ringer's solution and 0.9% saline in the treatment of rhabdomyolysis induced by doxylamine intoxication. Emerg Med J. 2007;24(4):276–80.
59. Kodadek L, Carmichael Ii SP, Seshadri A, Pathak A, Hoth J, Appelbaum R, Michetti CP, Gonzalez RP. Rhabdomyolysis: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document. Trauma Surg Acute Care Open. 2022;7(1):e000836.

Part III

Kidney Diseases Associated to Venomous Animals

8 Kidney Complications in Bothropic and Crotalic Envenomation

Jacqueline de Almeida Gonçalves Sachett, Marco Aurélio Sartim, Manuela Pucca, Lisele Brasileiro Martins, Thaís Pinto Nascimento, Valquir Silva dos Santos, Marcus Vinícius Guimarães de Lacerda, and Wuelton Marcelo Monteiro

8.1 Snakebite Envenomations in Brazil

Envenomation by venomous snakes is a public health problem due to its high morbidity and mortality rates and the fact that it affects more vulnerable populations with low socioeconomic status [1, 2]. The problem is more common in underdeveloped tropical countries in Africa, Asia, Latin America, and Oceania [3].

J. de Almeida Gonçalves Sachett · W. M. Monteiro (✉)
Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil

Universidade do Estado do Amazonas, Manaus, Amazonas, Brazil

M. A. Sartim
Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil

Universidade Federal do Amazonas, Manaus, Amazonas, Brazil

M. Pucca · L. B. Martins · T. P. Nascimento
V. S. dos Santos
Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil

M. V. G. de Lacerda
Fundação de Medicina Tropical Heitor Vieira Dourado, Dom Pedro, Manaus, Amazonas, Brazil

Instituto Leônidas & Maria Deane (ILMD/Fiocruz Amazônia), Manaus, Amazonas, Brazil

It is estimated that between 1,200,000 and 5,500,000 cases of snakebite accidents occur worldwide each year, of which 421,000 to 1,841,000 are actually envenomations, with 81,000 to 138,000 people dying and approximately 400,000 individuals suffering permanent sequelae [2, 4]. The highest rates of envenomation are estimated for South Asia, with approximately 121,000, followed by Southeast Asia, with 111,000, and Eastern Sub-Saharan Africa, with approximately 43,000 cases. The lowest numbers are estimated for Central Europe and Central Asia [5]. The regions of South and Southeast Asia and East Africa have the highest incidences, with fatalities being more frequent in South Asia and Eastern Sub-Saharan Africa [2]. India represents the country with the highest incidence of envenomations, followed by Sri Lanka, Vietnam, and Brazil [2].

In Brazil, a system for reporting snakebite accidents was implemented in 1986, making it mandatory to report them [6]. Between 2008 and 2017, 111,932 cases of snakebite accidents were reported in the country, the majority of which were caused by *Bothrops* 86.7% (97,097), followed by *Crotalus* 9.1% (10,238), *Lachesis* 3.1% (3426), and *Micrurus* 1.0% (1171) [7]. Among the Brazilian regions, the Central-West and North regions have the highest number of snakebite accidents, with the North region traditionally

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_8

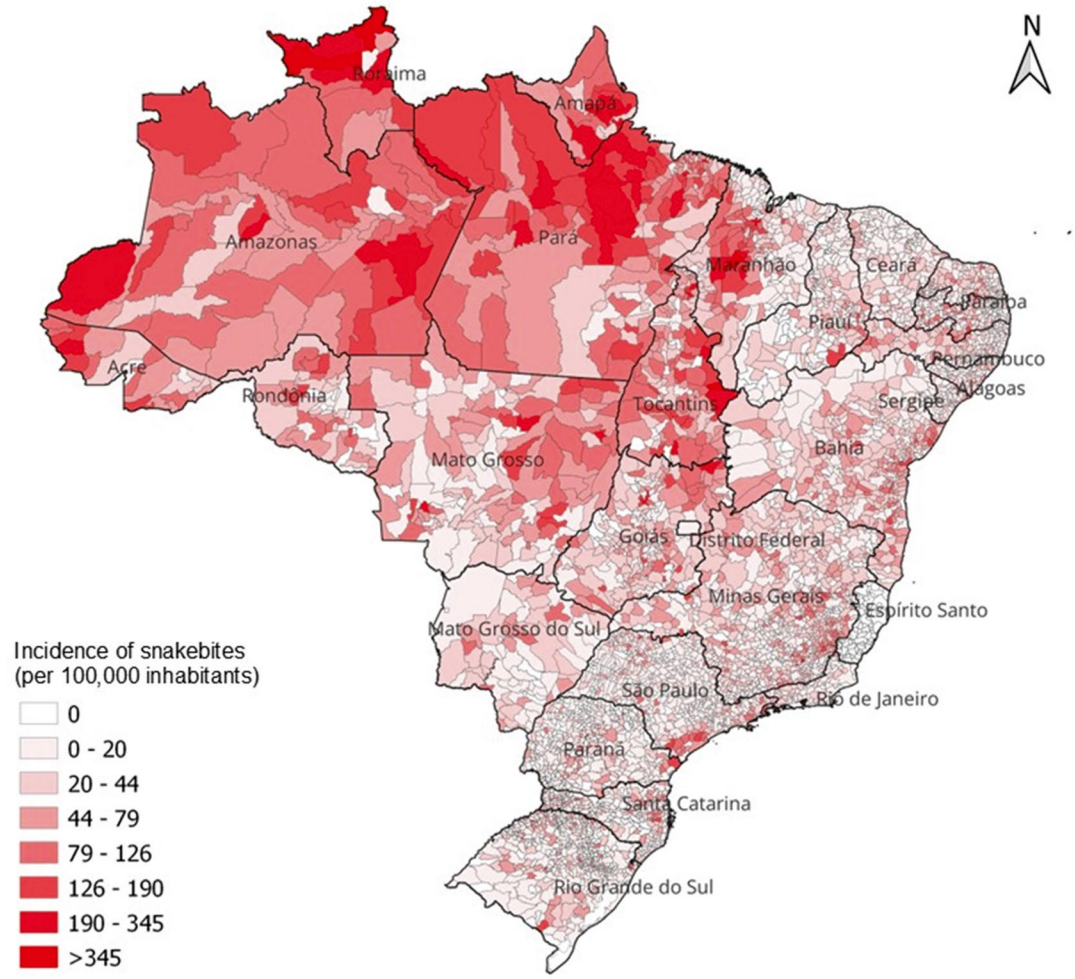


Fig. 8.1 Incidence of snakebite accidents (per 100,000 inhabitants) in Brazil, according to municipality of occurrence, in 2022 (DATASUS)

having the highest incidence (Fig. 8.1). The estimated national fatality rate is 0.52%, which may be aggravated in the Amazon, due to the mobility and communication difficulties existing in the region [8, 9]. When analyzed by type of accident, deaths are more frequent in crotalic accidents (1.54%), followed by lachetic (1.33%) and bothropic (0.38%) [7].

Some environmental factors also influence the incidence, such as rainfall, humidity, and temperature [10, 11]. During rainy periods, there is a reduction in dry land areas, which encourages snakes to migrate to areas occupied by workers who carry out agricultural activities [11]. In addition, this is the period in which snakes reproduce, which makes them more active. Regarding the seasonality of the diseases, depending on the region, there is generally a higher occurrence of cases between November and May [12].

Snakebite accidents with envenomation are defined as those caused by the inoculation of toxins produced and stored in the snake's venom glands, connected by a duct to the inoculating device [13, 14].

These snakes are called venomous snakes and are of medical interest [11]. Accidents

with species of the Viperidae and Elapidae families are most commonly reported with more serious symptoms [15]. The Brazilian territory has a diverse fauna of snakes, with approximately 265 species from 73 genera and 9 families cataloged [16]. Only the genera *Bothrops*, *Crotalus*, *Lachesis*, and *Micrurus* are involved in snakebite accidents with envenomation [17]. Despite being from different species, the components of the venom have similar clinical effects [18].

Much clinical evidence is lacking because most cases are treated in remote areas, without infrastructure that allows for the clinical description of milder cases or the carrying out of randomized clinical trials.

8.2 *Bothrops* Envenomation and Kidney Injury

8.2.1 The Genus *Bothrops*

In Brazil, the *Bothrops* genus causes the majority of snake envenomations and is distributed according to the type of accident as follows: *Bothrops*, *Bothropoides*, *Bothriopsis*, *Bothrocophias*, and *Rhinocerophis*. [19] Unlike what is observed in other regions, *Bothrops* genus is the main responsible for snakebite accidents in the Brazilian Amazon (87.0%) [20], with the species *Bothrops atrox* being responsible for approximately 80–90% of cases [21, 22].

In the Brazilian Amazon and Cerrado areas, there are 12 species of snakes belonging to the genera *Bothrops* and *Bothrocophias*. Five of them (*Bothrops lutzi*, *B. marmoratus*, *B. mattogrossensis*, *B. moojeni*, and *B. pauloensis*) are only found in the Cerrado areas, while the others are commonly found in Amazon rainforest environments (*Bothrops atrox*, *B. bilineatus*, *B. brazili*, *B. marajoensis*, *B. taeniatus*, *Bothrocophias hyoprora*, and *B. microphthalmus*) [23, 24] popularly known as jararaca, or even as surucucu, as it is used in the Alto Juruá region for adult snakes of the species *B. atrox* [25]. Accidents occur more frequently in other states in the northern region of Brazil. Even though they are from different species, the components of the venom present similarities in clinical effects [26]. The main representatives of the genus are listed below (Fig. 8.2).

8.2.2 *Bothrops* Envenomation: Pathophysiological, Clinical, and Therapeutic Aspects, Clinical Features, and Complications

Bothrops envenomation causes an intense local inflammatory response [28] and severe tissue damage [29]. It presents with the following manifestations: pain, edema, redness, bleeding, ecchymosis, blisters [6, 30], and occasionally lymph node infarction and myonecrosis [31]. Systemic effects include headache, nausea, vomiting, spontaneous hemorrhages (gum, nasal, digestive, hematuria, hematemesis), and, more rarely, disseminated intravascular coagulation and shock [18, 32]. Hemorrhagic manifestations can lead to hemodynamic destabilization [13, 30].

In snakebite, even with adequate administration of AV, local and systemic complications may develop. However, it has been observed that administration of AV more than 2 hours after the accident is associated with a higher risk of developing complications such as acute kidney injury (AKI), intracranial hemorrhage, and death [18].

The main local complications described are secondary infection (abscesses and cellulitis), necrosis, compartment syndrome, and permanent sequelae, such as functional deficit and amputations [18, 33]. Systemic complications such as sepsis and shock are rarer [18].

Some factors are associated with the development of complications: under 15 years and over 60 years and late admission to health services (>6 hours) [34].

Fig. 8.2 Representation of snakes belonging to the genus *Bothrops* and *Bothrocophias* involved in snakebite envenomations in the Brazilian Amazon and Brazilian Cerrado regions. (**a**) *Bothrocophias hyoprora*, (**b**) *Bothrops atrox*, (**c**) *Bothrops bilineatus bilineatus*, (**d**) *Bothrops brazili*, (**e**) *Bothrops moojeni*, and (**f**) *Bothrops mattogrossensis* [27]

8.2.3 Antivenom Treatment of *Bothrops* Envenomations

AV is the only specific treatment for snakebite accidents and must be administered in a timely manner, as it is highly effective in reversing systemic manifestations, which are the most serious [35].

The neutralization of the toxic effects of snake venom demonstrates the effectiveness of AV [36], since the available formulations may be aimed at a single species and/or genus or at several. According to this classification, we can catego-

Table 8.1 Classification according to severity and recommended antivenom therapy for *Bothrops* accidents [38]

Manifestations and Treatment	Classification		
	Light	Moderate	Serious
Locations Pain Edema Bruising	Absent or discreet	Clear	Intense
Systemic Severe bleeding Shock Anuria	Absent	Absent	Present
Clotting Time	Normal or altered	Normal or altered	Normal or altered
Serum therapy (number of vials)	2–4	4–8	12
Route of administration	Intravenous		

rize them into polyspecific (polyvalent) and monospecific (monovalent) [36].

Bothrops and *Bothrops-Lachesis* are the most commonly used due to the high frequency of accidents. Fractions of *Bothrops atrox* venom are not used in their production, but studies indicate their ability to neutralize the actions of the venom of this species [37].

In addition to AV treatment, complementary and supportive therapies are indicated depending on the clinical picture presented, with the use of analgesics, antibiotics, and hydration, among others [13].

In Brazil, treatment with antivenom (AV) is established based on the classification of cases, which may be mild, moderate, or severe. For this classification, the clinical picture and/or changes in laboratory tests presented by the victims are evaluated (Table 8.1) [13]. The coagulation time (CT) is a complementary parameter used to characterize the envenomation and the effectiveness of serum therapy, with normalization expected within 24 hours after administration of AV. In situations where coagulation is non-reversible, the administration of two additional ampoules is recommended [13].

8.2.4 *Bothrops* Venom and Its Mechanism of Action

Bothrops venom has a complex mixture of biologically active peptides and proteins that induce a series of effects, the main components being phospholipases A2 (PLA2s), metalloproteinases (SVMPs), serine proteinases (SVSPs), and hyaluronidases [39]. Phospholipases A2 act by producing free fatty acids and lysophospholipids, which can lead to myotoxicity [40]. SVMPs promote the disruption of vascular endothelium and inhibition of platelet aggregation, changes observed within minutes after inoculation, in vivo [37, 41–43]. SVSPs induce coagulant action by presenting thrombin-like activity, that is, they convert fibrinogen into fibrin [39]. Hyaluronidases act in the hydrolysis of oligosaccharides and N-acetylglucosamine, altering the structural and chemical properties of the extracellular matrix and contributing to the spread of the venom and consequently to its toxicity [44].

The action of *Bothrops* venom is characterized by the induction of local tissue lesions, such as edema and necrosis, and systemic changes such as dysregulation of blood coagulation. These pathophysiological phenomena are the result of the synergistic effects of these active proteins and enzymes present in the venoms [45, 46].

Myotoxicity caused by *Bothrops* envenomation causes elevated serum concentrations of myoglobin, creatine kinase, and potassium, which can lead to acute kidney injury [26, 47]. The venom also causes oxidative stress, triggering an increase in plasma levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), indicating hepatotoxicity; in addition, there have been reports of pulmonary alterations, such as respiratory failure [48–50]. However, kidney dysfunction is the most worrying systemic complication in *Bothrops* envenomation and can lead to acute glomerulonephritis, acute tubular necrosis, and acute kidney injury (AKI) [51].

8.2.5 Kidney Injury in *Bothrops* Envenomation: Clinical Aspects, Frequency, and Risk Factors

Kidney injury associated with AKI is a complex clinical disorder associated with morbidity and mortality. Despite technological advances in renal replacement therapy, AKI continues to be associated with severe prognoses, with sudden loss of kidney excretory function [52].

Among the genera causing accidents in Brazil, *Bothrops* accidents have a prevalence of between 1.4% and 38% of AKI [53] and in crotalic accidents of 10% and 29% [54, 55]. Mortality among those who have suffered envenomation varies between 13% and 19% [54].

In Amazonas, a study based on reported official data revealed that of the 9191 reported cases, the majority were caused by the *Bothrops* genus and approximately 12.6% of victims presented AKI [34]. In a reference unit in Manaus, of 212 patients who were victims of confirmed envenomation by the species *B. atrox*, 10.9% developed clinical symptoms of AKI [56]. And of 186 patients evaluated in the study, 24 (12.9%) developed AKI after 48 hours of the *Bothrops* accident, progressing to stage 1 AKI in 17 (70.8%), II in 3 (12.5%), and III in 4 (16.7%) of the patients [53].

Numerous variables are involved in the development of post-envenomation AKI: species of snake, age of the victim, children, due to their smaller body surface area, time of AV administration, and presence of comorbidities such as diabetes, hypertension, previous nephropathies, and coronary diseases [53, 54, 57, 58].

A more recent study demonstrated that individuals between 16 and 45 years of age have a lower risk of developing AKI, as an increase in the number of leukocytes and high serum urea levels were considered risk factors for this condition [59].

Ischemia, hemorrhage, and direct nephrotoxic action of the venom may be implicated in the development of AKI. In addition, victims of *Bothrops* envenomation may also develop chronic kidney disease, as shown in a study in which a patient with no previous comorbidities developed chronic kidney disease 2 years after an accident with a jararaca snake that was not treated with antivenom [60].

8.2.6 Mechanisms of Kidney Injury in *Bothrops* Envenomation

The kidneys are highly vascularized organs with an excretory function and are highly vulnerable to the direct action of toxins, since they are eliminated mainly via the kidneys [29]. The degree of nephrotoxicity will depend on several factors, such as the gender of the snake, the classification of the accident, and the time of exposure to the venom [5].

AKI is considered a broad clinical syndrome encompassing several etiologies, including acute tubular necrosis, prerenal azotemia, acute interstitial nephritis, acute glomerular and vasculitic kidney diseases, and acute postrenal obstructive nephropathy. Some of these conditions may coexist in the same patient [61, 62].

The pathogenesis of AKI has not yet been fully elucidated. However, it is understood that kidney injury can be triggered by the action of different ischemic and/or nephrotoxic mechanisms linked to the biological activity of the venom [26]. Some studies have proposed a multifactorial origin [63], with triggering factors acting in combination [18, 54, 58, 64]. The mechanisms involved are hemodynamic disturbances, immunological reactions, and nephrotoxic action of the venom per se [65].

Hemodynamic disturbances can be triggered by changes in hemostasis [55]. These changes are related to (1) activation of factor X and prothrombin, (2) conversion of fibrinogen to fibrin by thrombin-like substances, (3) thrombocytopenia, and (4) action of metalloproteinases, which compromise the integrity of the endothelial wall locally and systemically [43, 55]. Hemolysis and hematuria are involved in the process of kidney injury, due to the deposition and accumulation of hemoglobin and myoglobin cylinders, causing

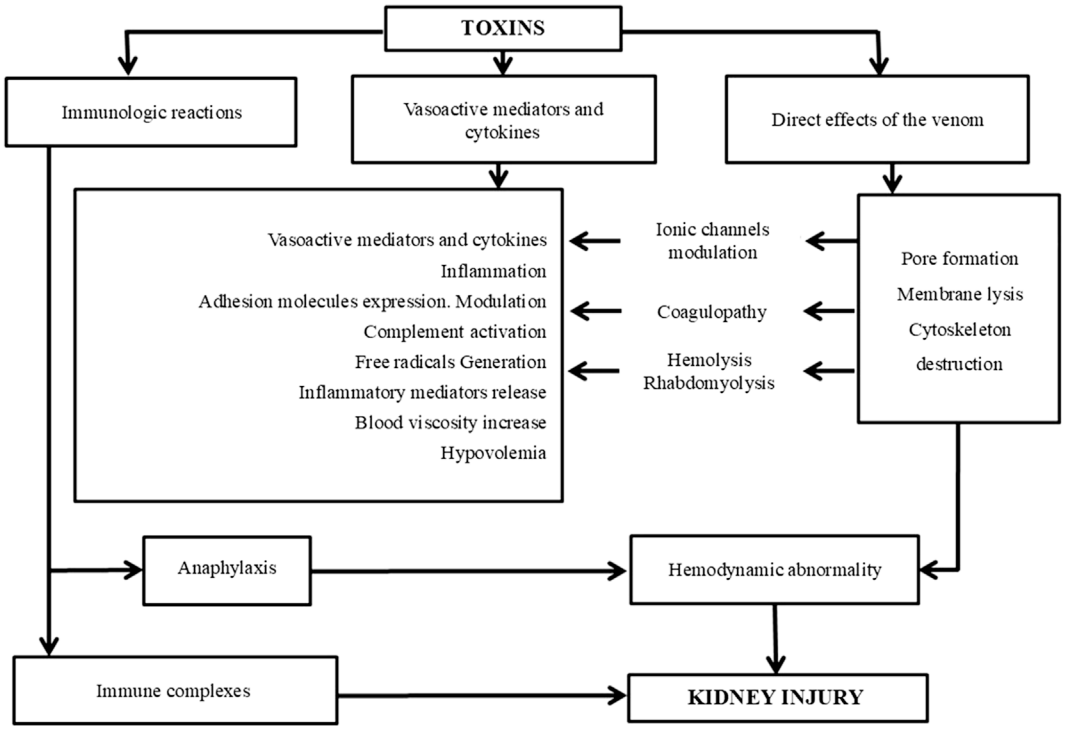


Fig. 8.3 Mechanism of kidney injury in snakebite envenomation. (Adapted from Albuquerque et al. (2013) [70])

obstruction and induction of vasoconstriction, culminating in ischemia and AKI [63].

Coagulation disorders can occur in patients who have suffered a *Bothrops* accident and plays an important role in the development of AKI, with the deposition of fibrin thrombi in the kidney parenchyma and microvasculature [66]. Approximately 25% of victims who developed AKI also presenting coagulopathy [57].

Of lesser relevance, the presence of C3 and IgM in the glomeruli suggests the formation of immune complexes and, consequently, may be associated with the development of glomerulonephritis [67].

Although there is controversy regarding the direct action of the venom on the kidney parenchyma, experimental models have been developed and have demonstrated the occurrence of this phenomenon in the presence of high concentrations of venom [65]. It is believed that hypoperfusion and nephrotoxicity act synergistically, increasing the frequency of acute tubular necrosis (ATN) [68]. The rapid onset of the condition, between 24 and 48 hours, suggests, however, direct action of the venom on the kidney tissue [57]. Some studies have indicated that the PLA_2 present in the venom promotes kidney alterations [67, 69].

Figure 8.3 illustrates the processes involved in the pathophysiology of kidney injury resulting from snakebite envenomation.

8.3 *Crotalus* Envenomation and Kidney Injury

8.3.1 The Species *Crotalus durissus*

Crotalic snakes in Brazil are represented by only one species, *Crotalus durissus* [71, 72]. Due to its wide geographic distribution in the country and the high severity of envenomations, the species is considered to be of medical importance. It is popularly known as the rattlesnake [71]. It is part of

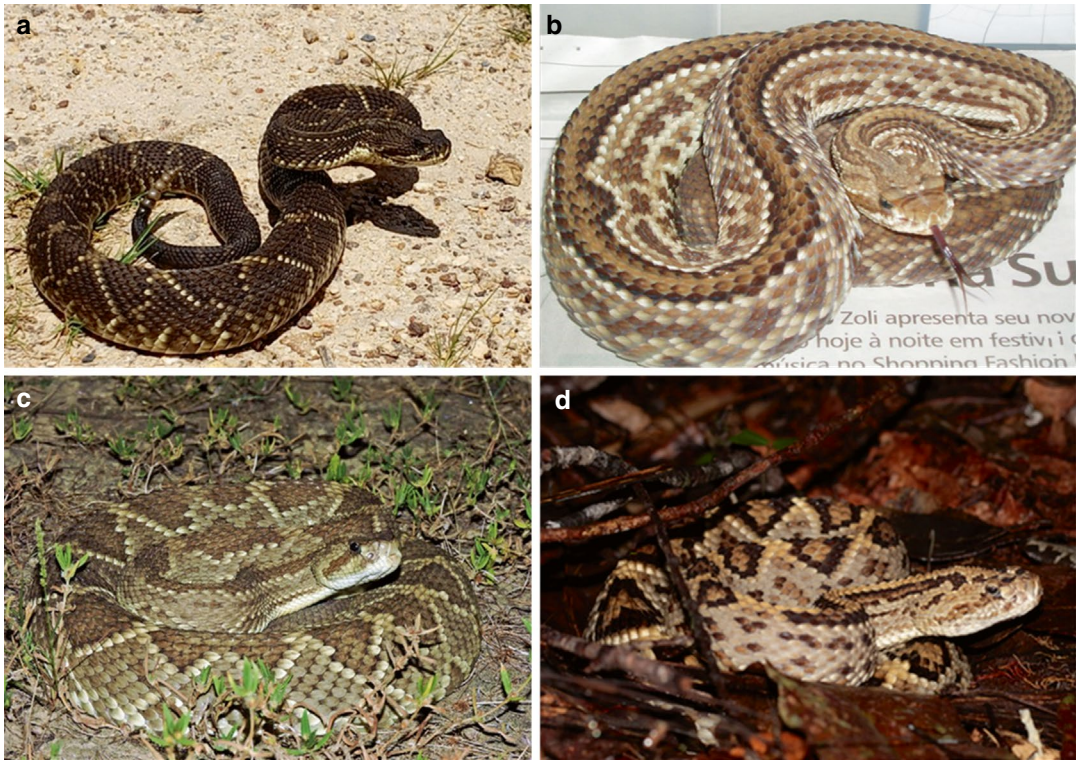


Fig. 8.4 Examples of representatives of snakes of the genus *Crotalus* of medical importance in Brazil. Source: Adapted from inaturalist.com. (**a**) *C. d. terrificus*. Photo: Henrique Costa. (**b**) *C. d. collilineatus*. Photo: Markus Kiefer. (**c**) *C. d. cascavella*. Photo: Sanjay Veiga. (**d**) *C. d. ruruima*. Photo: Matheus Costa

the Viperidae family and the Crotalinae subfamily. It has a total of 11 subspecies (*C. d. durissus*, *C. d. cascavella*, *C. d. collilineatus*, *C. d. cumanensis*, *C. d. marajoensis*, *C. d. maricelae*, *C. d. ruruima*, *C. d. terrificus*, *C. d. trigonicus*, *C. d. unicolor*, and *C. d. vegrandis*). They are frequently found in open habitats [71, 73].

The term "*Crotalus*" has Greek origins and means "rattle" or "castanets," referring to the characteristic tip of the tail of this snake. Its morphology is based on the presence of a loreal pit, vertical pupils, and keeled dorsal scales. On the neck, there are two dark stripes and its head is triangular. The standard body size of the species varies between 315 mm and 1345 mm [71, 73] (Fig. 8.4).

Their usual activities occur during the twilight hours of the night, and they are not usually active between 6 and 8 in the morning. They feed on small mammals and, to a lesser extent, lizards. They are viviparous and give birth to 11 to 13 young. These snakes usually flee from humans, but they can shake their tail rattle and coil up [71, 73].

8.3.2 Clinical Features and Complications of Crotalic Envenomation

In crotalic accidents, local manifestations may be absent or discreet, and edema, erythema, pain, and local paresthesia may be observed [74, 75]. Systemic symptoms are more frequent, with reports of nausea, headache, prostration, vomiting, agitation, variations in blood pressure, myasthenic facies, palpebral ptosis, and diplopia. The myotoxicity of crotalic venom is characterized by the presence of intense myalgia, myoglobinuria, rhabdomyolysis, fasciculations, and muscle paralysis [13, 74].

Table 8.2 Classification according to severity and recommended serum therapy for crotalic accidents [13]

Manifestations and treatment	Classification		
	Light	Moderate	Serious
Myasthenic facies/blurred vision	Absent or late	Discreet or obvious	Clear
Myalgia	Absent or discreet	Discreet	Intense
Red or brown urine	Absent	Not very evident or absent	Present
Oliguria/anuria	Absent	Absent	Present or absent
Serum therapy (number of vials)	5	10	20
Route of administration	Intravenous		

Neurotoxicity and myotoxicity are frequently reported in crotalic venom accidents. The neurotoxic action of the venom can lead to progressive descending paralysis, which is fatal when it involves bulbar and respiratory muscles [76]. Myotoxic action leads to rhabdomyolysis, which can result in myoglobinemia, hyperkalemia, and AKI. Hypotension and shock are other possible complications described [67].

8.3.3 Antivenom Treatment of Crotalic Envenomations

Treatment consists of the administration of a specific AV, which is crucial for the efficiency of treating crotalic envenomation [77]. AVs produced in Brazil use only one or two venoms from rattlesnake subspecies (*C. d. terrificus* 100% or *C. d. terrificus* 50% plus *C. d. collilineatus* 50%), and both have been used to treat envenomations caused by all six *Crotalus* subspecies in Brazil (*C. d. durissus*, *C. d. terrificus*, *C. d. cascavella*, *C. d. ruruima*, *C. d. marajoensis*, and *C. d. collilineatus*) [78, 79]. Dosage may vary depending on the severity of envenomation, although there are standardized dosage recommendations according to the severity of the case [17]. Severity classification can be seen in Table 8.2. Although, with appropriate, specific, and general treatment, most victims envenomated by rattlesnakes can recover and survive, there is some evidence to suggest that AV for *Crotalus* fails to neutralize all the deleterious actions of the venom [80].

8.3.4 Crotalic Venom and Its Mechanism of Action

Crotalic venom presents a composition of highly conserved toxins, such as phospholipases; serine proteases; lectin-like peptides (crotamine and bradykinin-potentiating peptides), in addition to those in lower concentrations such as L-amino acid oxidases; and metalloproteases, among others [81].

The set of toxic proteins and polypeptides in crotalic venom is represented by the substances crotoxin, crotamine, gyrotoxin, and convulxin, which cause changes in nerve endings, leading to neurotoxicity [75, 82]. Crotalic envenomations are often serious and, if not treated immediately, can be fatal. The composition of the venom influences the appearance of clinical manifestations [83].

The mixture is the result of the production of biochemical components essential for envenomation. The most important is crotoxin, formed by two subunits (phospholipase A2, with high enzymatic activity, and acidic peptide without toxic activity). This attribution is due to the fact that this enzyme has severe neurotoxic and nephrotoxic effects. Crotoxin, the most abundant toxin in the venom of the crotalic genus, acts on motor nerve endings, inhibiting the release of acetylcholine by nerve impulses by interfering with ion channels. Thus, there is neuromuscular blockade, resulting in motor and respiratory paralysis [81, 84].

The myotoxicity of this venom occurs due to the action of crotoxin and crotamine, which damage muscle tissue (rhabdomyolysis) [85]. Another action is coagulant, which occurs due to a substance similar to thrombin [75].

8.3.5 Kidney Injury in *Crotalus* Envenomation: Clinical Aspects, Frequency, and Risk Factors

Kidney injury is one of the main causes of mortality and sequelae in victims of crotalic envenomation. Due to its high vascularization, the kidney is highly susceptible to venom toxins, resulting in severe systemic reactions, with acute kidney injury (AKI) being one of the most serious complications of snakebite accidents [86].

Although *Bothrops* accidents are ten times more frequent than crotalic ones, the incidence of AKI is similar, which suggests greater nephrotoxicity of the venom of the genus *Crotalus* [87, 88].

8.3.6 Mechanisms of Kidney Injury in *Crotalus* Envenomation

Several mechanisms have been proposed to explain the kidney injury caused by *Crotalus* envenomation, including rhabdomyolysis, hemolysis, shock, intravascular coagulation, and possible direct nephrotoxic effect [76]. As the venom is excreted by the kidneys, the mechanisms of concentration and tubular transport favor the occurrence of direct cellular toxicity [89].

In crotalic venom, in addition to the mechanisms mentioned, rhabdomyolysis resulting from myotoxic action can cause myoglobinuria, hyperkalemia, and AKI. Crotoxin makes up 50% of the venom and explains the high occurrence of muscle injury and consequent AKI [55].

A study demonstrated that crotoxin can cause systemic lesions and skeletal muscle injuries, with this toxin being the main cause of acute nephrotoxicity associated with glomerular and tubular alterations [90].

Acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) are the most common pathological lesions seen in snakebites and can be reversed. In some cases, bilateral cortical necrosis (BCN) is an irreversible condition that progresses to chronic kidney disease (CKD) [54, 58]. However, it is observed that, in snakebites, the mechanism of kidney injury occurs through ATN [91].

8.4 Management of Kidney Injury in Snakebite Envenomation

The initial approach to a patient with kidney dysfunction, victim of a snakebite, involves general support measures, usual measures for patients with kidney injury, and specific measures, particularly when the condition evolves with the need for renal replacement therapy.

As general measures, it is important to evaluate factors that may aggravate already established kidney injury, such as the use of nephrotoxic drugs, especially non-hormonal anti-inflammatory drugs; the presence of associated bacterial infections in patients with cellulitis or abscesses, with treatment preferably guided by culture; and daily assessment of edema, when present, as well as arterial pulses and tissue perfusion. The emergence of compartment syndrome requires prompt surgical intervention. Clinical suspicion occurs in the presence of tense edema, changes in sensitivity, functional limitation, and changes in perfusion. Rhabdomyolysis is another possible complication, and when present, it worsens kidney injury. In these cases, using the same approach as for traumatic injuries, urine output should be maintained between 200 mL/h and 300 mL/h [92]. The use by laypeople of substances that stimulate vomiting and diarrhea in the injured patient should be avoided, because it can further increase dehydration and worsen AKI.

Among the usual measures in patients with kidney injury, care with volume replacement is a fundamental measure. To restore blood volume, infusion of 0.9% saline solution or Ringer's lactate solution is chosen. Hourly diuresis should be strictly controlled, especially in accidents classified as moderate or severe. Normally, adolescents and adults have a urine output greater than

Table 8.3 Classification table of stages of severity of kidney injury

AKI severity stages	Serum creatinine (Cr)	Diuresis
Stage 1	Increase of 0.3 mg/dL or increase of 150–200% of the baseline value (1.5 to 2 times)	<0.5 mL/kg/h for 6 hours
Stage 2	Increase of >200–300% from baseline (>2 to 3 times)	<0.5 mL/kg/h for 12 hours
Stage 3	300% increase from baseline (>3 times or serum Cr ≥4.0 mg/dL with an acute increase of at least 0.5 mg/dL)	<0.3 mL/kg/h for 24 hours or anuria for 12 hours

[a]Patients requiring dialysis are considered stage 3, regardless of the stage they were in at the start of dialysis therapy [94, 95]

0.5 mL/kg/h (30–40 mL/h) and children more than 1.0–2.0 mL/kg/h. It is important to emphasize that such replacement aims above all at achieving euvolemia, since bleeding and nausea with vomiting are added to large sequestrations of fluid in the interstitium of affected areas.

Other basic measures for the treatment of AKI include the correction of electrolyte disturbances with the use of diuretics and vasoactive drugs. Specific treatment with AV according to the accident classification is essential. Several studies have reported that late administration of AV is a risk factor for the development of AKI, and its early administration is capable of reversing kidney injuries [59].

Maintaining a high urinary flow rate protects the kidney parenchyma and maintains normal blood flow. However, it is essential to remember that, invariably, we are dealing with already established kidney injury and that renal replacement therapy will be necessary in cases of absence of diuresis (<0.5 mL/kg/h, in 12 h), persistent hypervolemia, and metabolic acidosis. Renal replacement therapy (RRT) is a specific treatment for severe cases of AKI, and peritoneal dialysis or hemodialysis may be chosen, despite the lack of evidence regarding the best option or ideal time to start it [58]. In most cases, patients recover kidney function after treatment. In a case series with 276 patients who were victims of snakebite, 15.2% developed AKI, of which 30% required dialysis and all recovered kidney function completely [64]. In a reference unit in Manaus, 12 patients underwent dialysis from 2013 to 2017, and all patients recovered total or partial renal function, without the need for maintenance dialysis, despite the late start of dialysis therapy, caused by delays in arrival at the hospital, with an average creatinine of 12.1 mg/dL (range 5.0 to 26.0 mg/dL), and no deaths (unpublished data).

In the presence of NCB, calcifications may occur in the kidney parenchyma, which may result in CKD [93], which is implicated in higher mortality rates [91]. In these cases, maintenance RRT will be necessary [91]. The severity of kidney injury is shown below (Table 8.3).

8.5 Chronic Kidney Disease in Snakebite Envenomation

Snakes of the genera *Bothrops*, *Crotalus*, and *Daboia* are the most commonly reported cases of ARI, and when not treated effectively and immediately, there is an increased chance of chronic kidney disease (CKD) [70, 96, 97]. CKD is associated with a high mortality rate, so preventive measures should be taken during the management of snakebite envenomations in order to avoid this common clinical picture [94].

Administration of AV within 6 hours of the accident is the only way to prevent the development of AKI and, consequently, CKD. However, as it progresses, it is necessary to comply with certain therapeutic measures, such as immediate hydration of patients to protect the kidneys and renal replacement therapy – dialysis [98].

Although there are still gaps in a more precise understanding of the disease (difficulty in standardized monitoring of victims and lack of specific methods to determine the severity of cases) [99], the literature shows that 37–41% of snakebite victims develop CKD [100, 101] and 5% are at risk of end-stage renal disease, although this can be prevented with regular

monitoring and treatment [100]. In most patients, recovery of kidney function is observed; however, many remain dependent on dialysis or have CKD [52].

In cases of established CKD, patients should be referred to a nephrologist for monitoring when they are in **stage 3** ((3a) GFR 45–59 mL/min/1.73 m² and (3b) 30–44 mL/min/1.73 m²), **stage 4** (GFR 15–29 mL/min/1.73 m²), and **stage 5** (GFR 15 mL/min/1.73 m^2) of CKD (pre-dialysis stage), as they will require monitoring by a multidisciplinary team for specialized care in CKD [102].

The benefits of dialysis make this strategy essential for patients with CKD. However, this therapy is not available at all medical care facilities, especially in remote and resource-poor regions [103]. In the Amazon, for example, victims of snakebite envenomation – generally riverside and indigenous people – need to travel to health facilities that have AV ampoules. Therefore, long distances and lack of resources increase the severity of cases and the occurrence of significant clinical complications during envenomation [104].

8.6 Take-Home Message

- The frequency of ARI in snakebite envenomations varies greatly between different studies due to the lack of standardization of diagnostic criteria and study designs.
- Snakebite envenomations occur more frequently in remote areas and among vulnerable populations, placing these populations at risk of severe ARI due to low access to antivenom treatment and early diagnosis and management of this systemic complication.
- Greater efforts are suggested to carry out studies on the pathophysiological mechanisms and search for biomarkers to support early and accurate diagnosis, management, and prognosis of ARI resulting from snake envenomation.
- Affordable and feasible diagnostic tests and therapeutic interventions should be urgently implemented in remote areas to decrease morbidity and mortality related to ARI in snake envenomations.

References

1. Warrell DA. Snake bite. Lancet. 2010;375:77–88.
2. Kasturiratne A, et al. The global burden of snakebite: a literature analysis and modeling based on regional estimates of envenomation and deaths. PLoS Med. 2008;5:e218.
3. Chippaux J-P. Guidelines for the production, control and regulation of snake antivenom immunoglobulins. Biol Aujourdhui. 2010;204:87–91.
4. The Lancet. Snakebite—emerging from the shadows of neglect. Lancet. 2019;393:2175.
5. Gutierrez JM et al. Snakebite envenoming. https://pubmed.ncbi.nlm.nih.gov/28905944/.
6. Cardoso J. Accidents caused by venomous animals in the coordination of zoonoses and venomous animals - comments and suggestions. Preprint at 1993.
7. da Brazil MS. Accidents caused by Venomous Animals. 2015. https://portalsinan.saude.gov.br/acidente-por-animais-peconhentos.
8. Gutiérrez JM, Williams D, Fan HW, Warrell DA. Snakebite envenomation from a global perspective: towards an integrated approach. Toxicon. 2010;56:1223–35.
9. Gutiérrez JM. Snakebite envenoming: A public health perspective. In Public health - Methodology, environmental and systems issues. IntechOpen; 2012. https://doi.org/10.5772/36076.
10. Warrell DA. Venomous bites, stings, and poisoning. Infect Dis Clin N Am. 2012;26:207–23.
11. Gutiérrez, JM, Theakston, DG & Warrel, DA Confronting the Neglected Problem of Snake Bite Envenomation: The Need for a Global Partnership | PLOS Medicine. 2006. https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0030150.
12. Chippaux J-P. Epidemiology of envenomations by terrestrial venomous animals in Brazil based on case reporting: from obvious facts to contingencies. J Venom Anim Toxins Incl Trop Dis. 2015;21:1–17.
13. Brazil. Manual of diagnosis and treatment of accidents caused by venomous animals. Brasília: Ministry of Health. Health Surveillance Secretariat. Department of Epidemiological Surveillance; 2001.
14. Franco F. Origin and diversity of snakes. In: Cardoso J, França FOS, Wen FH, Málaque C, Haddad VJ, editors. Venomous animals of Brazil: biology, clinic and therapy of accidents. Sarvier; 2009.
15. Warrel DA. Guidelines for the management of snakebites. 2010. https://www.who.int/publications-detail-redirect/9789290223774.

16. Melgarejo A. Venomous Snakes of Brazil. In: Savier editora. Venomous animals in Brazil: biology, clinic and therapy of accidents. 2009.
17. Brazil J. Manual of diagnosis and treatment of accidents caused by venomous animals. Rev baiana de saúde pública. 2014;76 https://doi.org/10.22278/2318-2660.1996.v1.n2.a1256.
18. Otero R, et al. Complications of Bothrops, Porthidium, and Bothriechis snakebites in Colombia. A clinical and epidemiological study of 39 cases attended in a university hospital. Toxicon. 2002;40:1107–14.
19. Fenwick A, Gutberlet R, Evans J, Parkinson C. Morphological and molecular evidence for phylogeny and classification of South American pitvipers, genera Bothrops, Bothriopsis, and Bothrocophias (Serpentes: Viperidae) | Request PDF. 2009. https://www.researchgate.net/publication/227536478_Morphological_and_molecular_evidence_for_phylogeny_and_classification_of_South_American_pitvipers_genera_Bothrops_Bothriopsis_and_Bothrocophias_Serpentes_Viperidae.
20. Brazil. Notifiable diseases information system - SINAN. Sinan Portal. 2019. https://portalsinan.saude.gov.br/.
21. Mendonça-da-Silva I, et al. Safety and efficacy of a freeze-dried trivalent antivenom for snakebites in the Brazilian Amazon: An open randomized controlled phase IIb clinical trial | PLOS Neglected Tropical Diseases. https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0006068.
22. Wen Hui F, et al. Snakebites and scorpion stings in the Brazilian Amazon: Identifying research priorities for a largely neglected problem | PLOS Neglected Tropical Diseases. 2015. https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003701.
23. Campbell JA, Lamar WW. The venomous reptiles of Latin America. Comstock Pub. Associates; 1989.
24. Bernarde PS. Venomous Snakes and Snakebites in Brazil. 2014. https://issuu.com/nipanga/docs/serpentes_pe__onhentas_isuu3.
25. da Siva AM, Monteiro WM, Bernarde PS. Popular names for bushmaster (Lachesis muta) and lancehead (Bothrops atrox) snakes in the Alto Juruá region: repercussions for clinical-epidemiological diagnosis and surveillance. Rev Soc Bras Med Trop. 2019;52:e20180140.
26. Albuquerque PL, et al. Clinical assessment and pathophysiology of Bothrops venom-related acute kidney injury. 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7359628/.
27. Alcantara JA, et al. Stepping into a dangerous quagmire: macroecological determinants of Bothrops envenomings, Brazilian Amazon. PLoS One. 2018;13:e0208532.
28. Moreira V, et al. Local inflammatory events induced by Bothrops atrox snake venom and the release of distinct classes of inflammatory mediators. Toxicon. 2012;60:12–20.
29. Cruz L, Vargas R, Lopes A. Snakebite envenomation and death in the developing world. Ethn Dis. 2009;19:42–6.
30. Oliveira F, Brito M, de Morais I, Fook S, de Albuquerque H. Accidents caused by Bothrops and Bothropoides in the state of Paraiba: epidemiological and clinical aspects. J Braz Soc Trop Med. 2010;43:662–7.
31. Mourão-de-Moura V, Mourão RH, Dos-Santos M. Snakebite accidents in the northern region of Brazil and the use of plant species as an alternative and complementary treatment to serum therapy. Scientia Amazonia. 2015;4:73–84.
32. Ribeiro L, Jorge M. Accidents caused by snakes of the Bothrops genus: series of 3,139 cases. J Braz Soc Trop Med. 1997;30:475–80.
33. Pinho F, Oliveira E, Faleiros F. Snakebite accident in the state of Goiás. J Assoc Brazil Doctor. 2004;50:93–6.
34. Feitosa E, et al. Older age and time to medical assistance are associated with severity and mortality of snakebites in the Brazilian Amazon: A Case-Control Study. PLoS One. 2015;10:1–15.
35. Warrell D. Guidelines for the Management of Snake-Bites, vol. 375; 2010. p. 77.
36. Wen F, Serotherapy H., in Venomous animals in Brazil: biology, clinic and therapy of accidents (ed. Cardoso, João Luiz Costa; França, Francisco Oscar de Siqueira; Fan, Hui Wen; Málaque, Ceila Maria Sant'Ana; Haddad Junior, V.), p. 432–41 (Sarvier, São Paulo, 2003).
37. Sparrow PPO, et al. Clinical trial of two antivenoms for the treatment of Bothrops and Lachesis bites in the north eastern Amazon region of Brazil. Trans R Soc Trop Med Hyg. 2004;98:28–42.
38. da Brazil, MS. Health Surveillance Guide. 2023.
39. Sousa LF, et al. Comparison of phylogeny, venom composition and neutralization by antivenom in diverse species of bothrops complex. PLoS Negl Trop Dis. 2013;7:e2442.
40. Kini RM. Excitement ahead: structure, function and mechanism of snake venom phospholipase A2 enzymes. Toxicon. 2003;42:827–40.
41. de Cunha EM, Martins O. Main chemical compounds present in the venoms of snakes of the genus Bothrops and Crotalus - A review. Electr J Educ Sci. 2012;2:2237–3462.
42. Luciano P, Barros-Silva G, Azevedo-Marques M. Fatal Bothrops accident. Medicine (Ribeirao Preto Online). 2009;42:61.
43. Gutiérrez JM, Rucavado A, Escalante T, Díaz C. Hemorrhage induced by snake venom metalloproteinases: biochemical and biophysical mechanisms involved in microvessel damage. Toxicon. 2005;45:997–1011.
44. Fox JW. A brief review of the scientific history of several lesser-known snake venom proteins: l-amino acid oxidases, hyaluronidases and phosphodiesterases. Toxicon. 2013;62:75–82.

45. Ownby CL. Locally acting agents: Myotoxins, hemorrhagic toxins and dermonecrotic. In: Handbook of toxicology, vol. 154; 1990.
46. Kamiguchi AS, Zuzel M, Theakston RDG. Snake venom metalloproteinases and disintegrins: interactions with cells. Braz J Med Biol Res. 1998;31:853–62.
47. Gutiérrez JM, et al. Why is skeletal muscle regeneration impaired after Myonecrosis induced by Viperid Snake venoms? - PubMed. Toxins. 2018;10 https://doi.org/10.3390/toxins10050182.
48. da Silva Souza A, et al. Snakebites as cause of deaths in the Western Brazilian Amazon: why and who dies? Deaths from snakebites in the Amazon. Toxicon. 2018;145:15–24.
49. Benvenuti LA, França FOS, Barbaro KC, Nunes JR, Cardoso JLC. Pulmonary haemorrhage causing rapid death after Bothrops jararacussu snakebite: a case report. Toxicon. 2003;42:331–4.
50. Sunitha K, et al. Inflammation and oxidative stress in viper bite: an insight within and beyond. Toxicon. 2015;98:89–97.
51. Sitprija V. Animal toxins and the kidney. Nat Clin Pract Nephrol. 2008;4:616–27.
52. Kliger AS, et al. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. Am J Kidney Dis. 2013;62:849–59.
53. Alves EC, et al. Predicting acute renal failure in Bothrops snakebite patients in a tertiary reference center, Western Brazilian Amazon. PLoS One. 2018;13:e0202361.
54. Albuquerque P, et al. Acute kidney injury caused by Crotalus and Bothrops snake venom: a review of epidemiology, clinical manifestations and treatment. Rev Inst Med Trop Sao Paulo. 2013;55:295–301.
55. Pinho F, Yu L, Burdmann E. Epidemiology of acute kidney injury in Latin America. Semin Nephrol. 2008;28:354–62.
56. Souza A. Accident caused by Bothrops atrox (LIN. 1758) snake in the state of Amazonas: study of 212 cases with identification of the snake. J Trop Pathol. 2002;31:259–68.
57. Danis R, et al. Snakebite-induced acute kidney injury: data from Southeast Anatolia. Ren Fail. 2008;30:51–5.
58. Sgrignolli L, Mendes G, Carlos C, Burdmann E. Acute kidney injury caused by Bothrops snake venom. Nephron. 2011;119:131–8.
59. Brasileiro-Martins LM, et al. The severity of acute kidney injury correlates with plasma venom levels in Bothrops atrox envenomes. Toxicon. 2022;219:106924.
60. Sitprija V. Snakebite nephropathy. Nephrology (Carlton). 2006;11:442–8.
61. Bellomo R, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204–12.
62. Mehta RL, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
63. Chugh K, et al. Acute renal failure following poisonous snakebite. Am J Kidney Dis. 1984;IV:30–8.
64. Albuquerque P, et al. Acute kidney injury after snakebite accident treated in a tertiary care center. Nephrology. 2014;19:1–23.
65. de Castro I, Burdmann E, Seguro A, Yu L. Bothrops venom induces direct renal tubular injury: role for lipid peroxidation and prevention by antivenom. Toxicon. 2004;43:833–9.
66. Athappan G, Balaji M, Navaneethan U, Thirumalikolundusubramanian P. Acute renal failure in Snake envenomation: A large prospective study. Saudi J Kidney Dis Transpl. 2008;19:404–10.
67. Kanjanabuch T, Sitprija V. Snakebite nephrotoxicity in Asia. Semin Nephrol. 2008;28:363–72.
68. Lameire N, Biesen W, Vanholder R. Acute renal failure. Lancet. 2005;365:417–30.
69. Barbosa PSF, et al. Renal toxicity of Bothrops moojeni snake venom and its main myotoxins. Toxicon. 2002;40:1427–35.
70. Albuquerque PLMM, et al. Acute kidney injury caused by Crotalus and Bothrops snake venom: a review of epidemiology, clinical manifestations and treatment. Rev Med Trop Inst São Paulo. 2013;55:295–301.
71. da Silva-Júnior LN, et al. Geographic variation of individual venom profile of Crotalus durissus snakes. J Venom Anim Toxins Incl Trop Dis. 2020;26:e20200016.
72. de Oliveira IS, Pucca MB, Sampaio SV, Arantes EC. Antivenomic approach of different Crotalus durissus collilineatus venoms. J Venom Anim Toxins incl Trop Dis. 2018;24:34.
73. Pucca MB, et al. Crotalus Durissus Ruruima: current knowledge on natural history, medical importance, and clinical Toxinology. Front Immunol. 2021;12
74. Jorge M, Ribeiro L. Epidemiology and clinical picture of the South American rattlesnake (Crotalus durissus). Rev Inst Med Trop Sao Paulo. 1992;34:347–54.
75. Pardal PPO, Silva CLQ, Hoshino SSN, Pinheiro PR. Rattlesnake accident (Crotalus sp.) in Ponta de Pedras, Marajó Island, Pará - case report. Paraense Medical School. 2007;20:51–6.
76. Daher E, Fernandes T, Aguiar C. Crotalus poisoning: Epidemiology, acute renal failure and other clinical manifestations | Request PDF. Electronic Medical Research Journal; 2008.
77. Frare BT, et al. Clinical, laboratory, and therapeutic aspects of Crotalus durissus (South American Rattlesnake) victims: A literature review. Biomed Res Int. 2019;2019:1345923.

78. Baum RA, et al. Crotalus durissus terrificus (viperidae; crotalinae) envenomation: respiratory failure and treatment with antivipmyn TRI® antivenom. Toxicon. 2019;163:32–5.
79. Amaral CF, Campolina D, Dias MB, Bueno CM, Rezende NA. Tourniquet ineffectiveness to reduce the severity of envenomation after Crotalus durissus snake bite in Belo Horizonte, Minas Gerais, Brazil. Toxicon. 1998;36:805–8.
80. Dos Santos MC, Ferreira LCL, Da Silva WD, Furtado M. FD characterization of activities Biologics of the 'yellow' and 'white' venoms of Crotalus durissus ruruima compared with the venom of Crotalus durissus terrificus. Neutralizing power of them antivenoms against Crotalus venoms durissus ruruima. Toxicon. 1993;31: 1459–69.
81. Calvete JJ, et al. Snake venomics of the Central American rattlesnake Crotalus simus and the South American Crotalus durissus complex points to neurotoxicity as an adaptive paedomorphic trend along Crotalus dispersal in South America. J Proteome Res. 2010;9:528–44.
82. Caiaffa W, Vlahov D, Antunes C, de Oliveira H, Diniz C. Snake bite and antivenom complications in Belo Horizonte, Brazil. Trans R Soc Trop Med Hyg. 1994;88:81–5.
83. de Carvalho AEZ, et al. Crotalus durissus ruruima Snake venom and a phospholipase A2 isolated from this venom elicit macrophages to form lipid droplets and synthesize inflammatory lipid mediators. J Immunol Res. 2019;2019:2745286.
84. Faure G, Bon C. Crotoxin, a phospholipase A2 neurotoxin from the South American rattlesnake Crotalus durissus terrificus: purification of several isoforms and comparison of their molecular structure and of their biological activities. Biochemistry. 1988;27:730–8.
85. Azevedo-Marques M, Cupo P, SE H. Accidents caused by venomous animals: Venomous Snakes. Medicine of Ribeirão Preto. 2003;36:480–9.
86. Sitprija V, Sitprija S. Renal effects and injury induced by animal toxins. Toxicon. 2012;60:943–53.
87. Silveira PV, de Nishioka SA. South American rattlesnake bite in a Brazilian teaching hospital. Clinical and epidemiological study of 87 cases, with analysis of factors predictive of renal failure. Trans R Soc Trop Med Hyg. 1992;86:562–4.
88. de Castro I, Burdmann EA, Seguro AC, Yu L. Bothrops venom induces direct renal tubular injury: role for lipid peroxidation and prevention by antivenom. Toxicon. 2004;43:833–9.
89. Santos M, Farani M, Rocha P. Acute kidney injury in Bothrops sp. and Crotalus sp. envenomation: critical review of the literature. J Bras Nephrol. 2009;31:132–8.
90. Monteiro HS, da Silva IM, Martins AM, Fonteles MC. Actions of Crotalus durissus terrificus venom and crotoxin on the isolated rat kidney. Braz J Med Biol Res. 2001;34:1347–52.
91. Santos M, Farani M, Rocha P. Acute renal failure in Bothrops snakebites sp. and Crotalus sp.: review and critical analysis of the literature. J Braz Nephrol Assoc. 2009;31:132–8.
92. Stanley M, Chippa V, Aeddula NR, Quintanilla Rodriguez BS, Adigun R. Rhabdomyolysis. In: StatPearls. Treasure Island: StatPearls Publishing; 2024.
93. Quino H, Velázques M, Hurtado M, Urcia J, Hurtado A. Ofidismo y Falla Renal. Peruvian Soc Intern Med Bull. 1995;8:23–6.
94. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179–84.
95. Yu L, dos Santos BFC, Burdmann E of A, Suassuna, JHR & Batista. PBP Acute Renal Failure. J Bras Nephrol. 2007;29
96. Pinho FMO, Yu L, Burdmann EA. Snakebite-induced acute kidney injury in Latin America. Semin Nephrol. 2008;28:354–62.
97. Kularatne SAM, et al. Revisiting Russell's viper (Daboia russelii) bite in Sri Lanka: is abdominal pain an early feature of systemic envenomation? PLoS One. 2014;9:e90198.
98. Pucca MB, et al. Chronic kidney failure following lancehead bite envenomation: a clinical report from the Amazon region. J Venom Anim Toxins Incl Trop Dis. 26:e20200083.
99. Waiddyanatha S, Silva A, Siribaddana S, Isbister GK. Long-term Effects of Snake Envenomation Toxins (Basel). 2019;11:193.
100. Waikhom R, et al. Long-term renal outcome of snake bite and acute kidney injury: a single-center experience. Ren Fail. 2012;34:271–4.
101. Herath HMNJ, et al. Chronic kidney disease in snake envenomated patients with acute kidney injury in Sri Lanka: a descriptive study. Postgrad Med J. 2012;88:138–42.
102. Brazil, Ministry of Health. Ordinance No. 1,675 of June 7, 2018. 7.
103. Wong CKH, et al. Lifetime cost-effectiveness analysis of first-line dialysis modalities for patients with end-stage renal disease under peritoneal dialysis first policy. BMC Nephrol. 2020;21:42.
104. Cristino JS, et al. A painful journey to antivenom: The therapeutic itinerary of snakebite patients in the Brazilian Amazon. 2021. https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0009245.

9 Nephropathy Caused by Scorpion Stings

Edgar Sanclemente-Paz

9.1 Epidemiology

Scorpions are the oldest species of terrestrial animals and have maintained their morphology for more than 400 million years of evolution. They are present on all continents except Antarctica [1].

In Asia and Africa, there are the genera *Lepturus*, *Parabuthus*, *Androctonus*, *Mesobuthus*, and *Leiurus*, which represent a major public health problem in these regions due to the deleterious effects on important organs of the human economy [2].

In South America, Brazil and, in Central America, Mexico are the countries with the highest number of cases of scorpion stings, which constitute a serious public health problem. To a lesser extent, they are represented in North America and South America [3–13].

The genera *Centruroides* and *Tityus* are the most dangerous because they are associated with the appearance of systemic effects that can lead to death (Fig. 9.1).

Scorpion stings are the second most common cause of animal toxin poisoning in some regions, after snakebites [14].

Fig. 9.1 Scorpions of the genera *Centruroides* and *Tityus*. (Courtesy of Dr. Rubina Naqvi)

E. Sanclemente-Paz (✉)
Department of Internal Medicine,
Faculty of Medicine, University of Cauca,
Popayán, Cauca, Colombia
e-mail: esanclemente@imbanaco.com.co

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_9

9.2 Components of Venom and Toxins

Scorpion venom components have variable concentrations of neurotoxins, cardiotoxins, nephrotoxins, and hemolytic toxins. Its compounds—phosphodiesterases, phospholipases, hyaluronidases, glycosaminoglycans, histamine, serotonin, tryptophan, toxins that block potassium and calcium channels, and cytokine-releasing substances—are the cause of lesions in several organs, including the kidney [15, 16]. There is evidence of the role of cytokines in scorpion envenomation due to their pro-inflammatory effects, especially interleukins 1 and 6, IFN-ϒ, and tumor necrosis factor, which can lead to multi-organ failure [17].

Scorpion venom has several components that act on the cardiovascular system, including natriuretic peptides; sarafotoxins, which are potent vasoconstrictors; and other peptides that enhance bradykinin with hypotensive properties [18, 19].

Its composition includes phospholipases, metalloproteases, hyaluronidases, and proteolytic enzymes. Its toxins (NaTx, KTx, and CaTx) have specificity and high affinity for the proteins of the sodium, potassium, and calcium ion channel receptors. Alpha toxins in venom delay Na + channel inactivation, which increases intracellular sodium, which in turn increases Ca++ entry through Na + -Ca++ exchange via long calcium channels [20–27].

The main toxins contained in scorpion venoms are the following: maurotoxin, kaliotoxin, tityustoxin, charybdotoxin, fungus toxin, iberiotoxin, margotoxin, noxiustoxin, and BTK2. These substances block voltage-dependent K+ channels, ATP, ROMK1, Kv1.2, and Kv1.3 [28–36]. The venom of the Colombian scorpion *Centruroides margaritatus* contains a peptide (CM28), which has a unique primary structure that inhibits potassium channels Kv1.2 and Kv1.3 [37, 38].

The peptide Cm39 (α-KTx4.8) from the same venom has inhibitory action on the calcium-activated potassium channels Kca2.2 and Kca3.1 [39].

9.3 Nephrotoxicity of the Venom

Scorpion venom produces direct toxicity on renal structures by releasing various enzymes and cytokines that constrict the afferent arteriole of the glomerulus by activating the α-adrenoceptors due to the blockage of potassium channels causing depolarization and contraction of vascular smooth muscle [24, 40, 41].

In vitro studies with proximal tubule cell culture showed apoptosis by activation of caspases and oxidative stress with the venom [42].

Experimental studies with the injection of the venom of the South American scorpion *Tityus serrulatus* showed a significant impact on renal hemodynamics by vasoconstriction with a decrease in the glomerular filtration rate without major changes in tubular transport. Another study carried out on rat kidneys, isolated and perfused with the venom, showed a lesion of tubular necrosis and an increased excretion of electrolytes [43–45].

A recent investigation with the venom of the Colombian scorpion *Centruroides margaritatus*, in isolated kidneys of rats and in renal cell culture (MDCK), revealed its deleterious action on renal function and its toxicity primarily on the cells of the proximal tubule of the kidney [46].

Acute kidney injury by scorpion venom is the result of renal ischemia due to intense vasoconstriction and an inflammatory reaction due to proinflammatory cytokines and their mediators that cause oxidative stress [47–50].

Renal vasoconstriction is not only produced by a catecholamine storm but also by angiotensin II, by virtue of a peptidase similar to the converting enzyme present in the venom of some spe-

cies. In addition, there is a direct action on vascular ion channels. Increased aldosterone is another cause of hypertension [51, 52].

Blockade of K+ channels in the tubules decreases potassium excretion, increasing serum K+ that promotes the release of aldosterone, which produces an increase in potassium excretion through ROMK2 and ROMK3 channels, which are not blocked by venom. The presence of angiotensin-converting enzyme inhibitors in some species of scorpions contributes to hyperkalemia [53, 54].

These hemodynamic changes due to the action of venom on ion channels produce vasoconstriction and ischemia of the kidney and can lead to acute kidney injury due to tubular necrosis, in addition to intravascular hemolysis. Hemolytic-uremic syndrome with thrombotic microangiopathy can also occur due to deficiency of the ADAMTS factor 13, a disintegrin, and metalloproteinase involved in coagulation [18, 40, 55–67]. Cases of acute kidney injury, tubulointerstitial nephritis, and nephrotic syndrome secondary to scorpion stings have been described [68, 69] (Figs. 9.2, 9.3, 9.4, and 9.5).

A study in Iran, with 232 adult patients who are victims of scorpion stings (*Hemiscorpius lepturus*), evidenced that 6% presented acute kidney injury due to disseminated intravascular coagulation and hemolysis [70].

Another study, conducted with 250 children from Iran, with scorpion stings *Hemiscorpius lepturus*, Hemiscorpius lepturus, evidenced that 27.4% developed acute kidney injury secondary to pigmentary nephropathy due to microangiopathic hemolytic anemia. Proteinuria, hematuria, and hemoglobinuria were frequent findings in these patients [71].

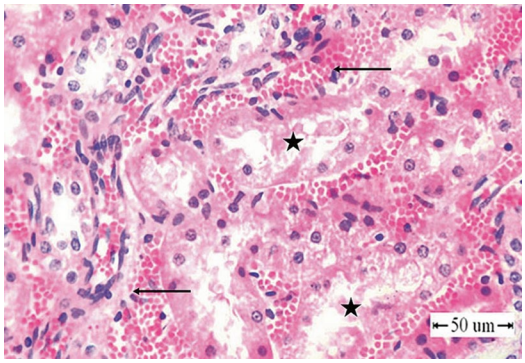


Fig. 9.2 Acute kidney injury due to scorpion sting—acute tubular necrosis and interstitial hemorrhage. (Reproduced, with permission, from Afifi et al. [45])

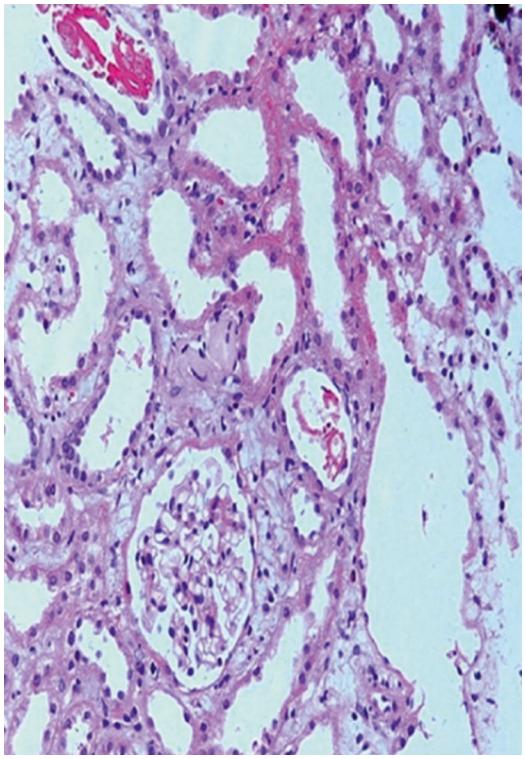


Fig. 9.3 Acute kidney injury due to scorpion sting—acute tubular necrosis. (Reproduced, with permission, from Naqvi et al. [63])

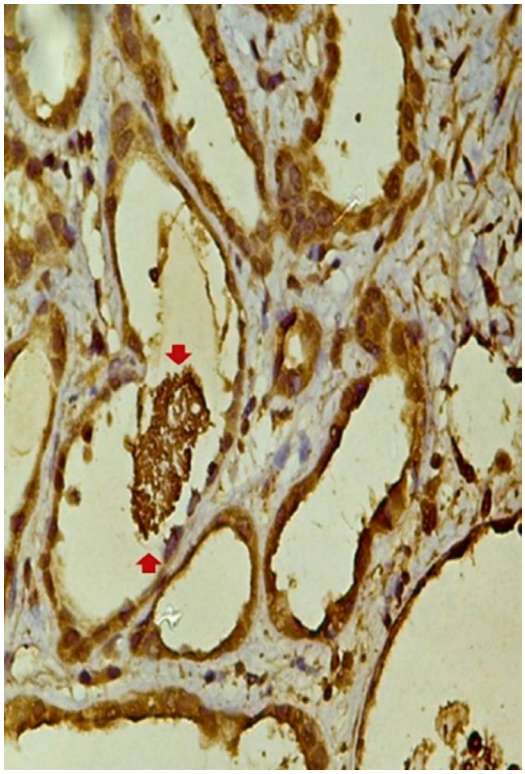


Fig. 9.4 Acute kidney injury due to scorpion sting—acute tubular necrosis; myoglobin cylinder. (Reproduced, with permission, from Naqvi et al. [63])

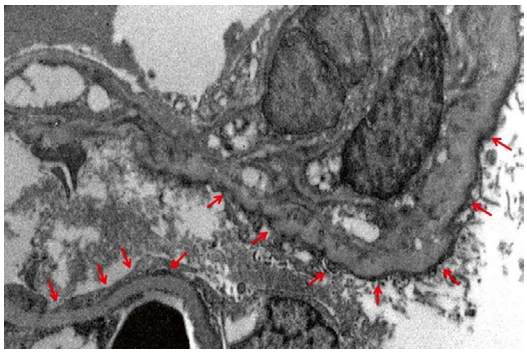


Fig. 9.5 Nephropathy caused by scorpion sting—minimal change disease (arrows: podocyte fusion), nephrotic syndrome. (Courtesy by Dr. R. Ram. Reproduced, with permission, from Boju et al. [69])

9.4 Clinical Manifestations

The clinical picture of scorpion sting envenoming is arterial hypertension secondary to stimulation of catecholamines and the renin-angiotensin-aldosterone axis. Hyperglycemia, hypocalcemia, and hypomagnesemia may be observed. From the renal point of view, a decrease in kidney blood flow and toxic nephropathy due to rhabdomyolysis and tubular necrosis are observed [72–74].

9.5 Treatment

Treatment in severe cases is aimed at correcting hydroelectrolytic disorders and hyperglycemia and the use of anti-scorpion serum. Hemodynamic-ventilation support and renal replacement therapy may be required in severe cases with acute kidney injury [75–80].

Exchange transfusion and plasmapheresis have also been used in cases of disseminated intravascular coagulation secondary to scorpion (*Hemiscorpius lepturus*) stings [81, 82].

It has been suggested that some pediatric patients may develop chronic kidney disease secondary to the acute episode of scorpion envenomation with hemolytic-uremic syndrome [83–85].

9.6 Clinical Applications of Scorpion Venoms

They have shown anti-inflammatory, anticoagulant, antifungal, antimicrobial, and anticancer properties, as well as their possible usefulness in the treatment of autoimmune diseases [86–96].

9.7 Take-Home Message

- Special care should be taken in children and the elderly to avoid scorpion stings, as they present a more severe clinical picture and greater complications.
- Keep anti-scorpion serum available for severe cases of scorpionism.

References

1. Cao Z, Di Z, Wu Y, Li W. Overview of scorpion species from China and their toxins. Toxins (Basel). 2014;6:796–815.
2. Kumar R. An update on epidemiology and management practices of Scorpion envenomation in India. J Family Med Prim Care. 2022;11:4932–5.
3. Borges A, Miranda R, Pascale J. Scorpionism in Central America, with special reference to the case of Panama. J Venom Anim Toxins incl Trop Dis. 2012;18:130–43.
4. Furtado S da S, Belmino JFB, Diniz AGQ, Leite R de S. Epidemiology of scorpion envenomation in the State of Ceará, northeastern Brazil. Rev Inst Med Trop Sao Paulo. 2016;58:15.
5. Santibáñez-López CE, Francke OF, Ureta C, Possani LD. Scorpions from Mexico: from species diversity to venom complexity. Toxins (Basel). 2015;8:2.
6. Marinkelle CJ, Stahnke HL. Toxicological and clinical studies on Centruroides margaritatus (Gervais), a common scorpion in western Colombia. J Med Entomol. 1965;2:197–9.
7. Borges A, Morales M, Loor W, Delgado M. Scorpionism in Ecuador: first report of severe and fatal envenoming cases from northern Manabí by Tityus asthenes Pocock. Toxicon. 2015;105:56–61.
8. Ortiz MS. Principales artrópodos de importancia médica. I. Scorpiones, Araneae y Acari Revista Ciencias. 2016;11.
9. Román JP, García F, Medina D, et al. Scorpion envenoming in Morona Santiago, Amazonian Ecuador: molecular phylogenetics confirms involvement of the Tityus obscurus group. Acta Trop. 2018;178:1–9.
10. Ward MJ, Ellsworth SA, Nystrom GS. A global accounting of medically significant scorpions: epidemiology, major toxins, and comparative resources in harmless counterparts. Toxicon. 2018;151:137–55.
11. González-Santillán E, Possani LD. North American scorpion species of public health importance with a reappraisal of historical epidemiology. Acta Trop. 2018;187:264–74.
12. Martins JG, Santos GC, de Procópio REL, et al. Scorpion species of medical importance in the Brazilian Amazon: a review to identify knowledge gaps. J Venom Anim Toxins Incl Trop Dis. 2021;27:e20210012.
13. Cáceres E, Medina M, Olmedo C, et al. La importancia médica del escorpionismo en Paraguay: revisión de la falla multisistémica asociada al envenenamiento y contribución a su diagnóstico diferencial. Revista de la Sociedad Científica del Paraguay. 2022;27:122–52.
14. Kularatne SAM, Senanayake N. Venomous snake bites, scorpions, and spiders. Handb Clin Neurol. 2014;120:987–1001.
15. Al-Asmari AK, Kunnathodi F, Al Saadon K, Idris MM. Elemental analysis of scorpion venoms. J Venom Res. 2016;7:16–20.
16. Kazemi-Lomedasht F, Khalaj V, Bagheri KP, et al. The first report on transcriptome analysis of the venom gland of Iranian scorpion, Hemiscorpius lepturus. Toxicon. 2017;125:123–30.
17. Petricevich VL. Scorpion venom and the inflammatory response. Mediat Inflamm. 2010;2010:903295.
18. Machado RJA, Junior LGM, Monteiro NKV, et al. Homology modeling, vasorelaxant and bradykinin-potentiating activities of a novel hypotensin found in the scorpion venom from Tityus stigmurus. Toxicon. 2015;101:11–8.
19. Chen R, Chung S-H. Computational studies of venom peptides targeting potassium channels. Toxins (Basel). 2015;7:5194–211.
20. Quintero-Hernández V, Jiménez-Vargas JM, Gurrola GB, et al. Scorpion venom components that affect ion-channels function. Toxicon. 2013;76:328–42.
21. Kuzmenkov AI, Grishin EV, Vassilevski AA. Diversity of Potassium Channel ligands: focus on scorpion toxins. Biochemistry (Mosc). 2015;80:1764–99.
22. Kuzmenkov AI, Krylov NA, Chugunov AO, et al. Kalium: a database of potassium channel toxins from scorpion venom. Database (Oxford). 2016;2016:baw056.
23. Yu M, Liu S, Sun P, et al. Peptide toxins and small-molecule blockers of BK channels. Acta Pharmacol Sin. 2016;37:56–66.
24. Martin-Eauclaire M-F, Pimenta AMC, Bougis PE, De Lima M-E. Potassium channel blockers from the venom of the Brazilian scorpion Tityus serrulatus (Lutz and Mello, 1922). Toxicon. 2016;119:253–65.
25. Sitprija V, Sitprija S. Animal toxins and renal ion transport: another dimension in tropical nephrology. Nephrology (Carlton). 2016;21:355–62.
26. Estrada-Gómez S, Gomez-Rave L, Vargas-Muñoz LJ, van der Meijden A. Characterizing the biological and biochemical profile of six different scorpion venoms from the Buthidae and Scorpionidae family. Toxicon. 2017;130:104–15.
27. Martin-Eauclaire M-F, Bougis PE, de Lima ME. Ts1 from the Brazilian scorpion Tityus serrulatus: a half-century of studies on a multifunctional beta like-toxin. Toxicon. 2018;152:106–20.

28. Costal-Oliveira F, Duarte CG, Machado de Avila RA, et al. General biochemical and immunological characteristics of the venom from Peruvian scorpion Hadruroides lunatus. Toxicon. 2012;60:934–42.
29. Ozawa S, Kimura T, Nozaki T, et al. Structural basis for the inhibition of voltage-dependent K+ channel by gating modifier toxin. Sci Rep. 2015;5:14226.
30. Meng L, Xie Z, Zhang Q, et al. Scorpion potassium channel-blocking defensin highlights a functional link with neurotoxin. J Biol Chem. 2016;291:7097–106.
31. Ladjel-Mendil A, Martin-Eauclaire M-F, Laraba-Djebari F. Neuro-modulation of immuno-endocrine response induced by kaliotoxin of Androctonus scorpion venom. J Biochem Mol Toxicol. 2016;30:580–7.
32. Olamendi-Portugal T, Bartok A, Zamudio-Zuñiga F, et al. Isolation, chemical and functional characterization of several new K(+)-channel blocking peptides from the venom of the scorpion Centruroides tecomanus. Toxicon. 2016;115:1–12.
33. Cid Uribe JI, Jiménez Vargas JM, Ferreira Batista CV, et al. Comparative proteomic analysis of female and male venoms from the Mexican scorpion Centruroides limpidus: novel components found. Toxicon. 2017;125:91–8.
34. Jiménez-Vargas JM, Possani LD, Luna-Ramírez K. Arthropod toxins acting on neuronal potassium channels. Neuropharmacology. 2017;127:139–60.
35. Nekrasova O, Yakimov S, Kirpichnikov M, Feofanov A. Recombinant scorpion toxins: focus on four-disulfide peptide blockers of Kv1-channels. Bioengineered. 2018;9:25–9.
36. Beltrán-Vidal J, Carcamo-Noriega E, Pastor N, et al. Colombian scorpion Centruroides margaritatus: purification and characterization of a gamma potassium toxin with full-block activity on the hERG1 channel. Toxins (Basel). 2021;13:407.
37. Naseem MU, Beltrán-Vidal J, Carcamo-Noriega E, et al. A novel peptide from the venom of Centruroides margaritatus has unique primary structure and inhibits Kv1.2 and Kv1.3 with high affinity. Biophys J. 2022;121:389a.
38. Naseem MU, Gurrola-Briones G, Romero-Imbachi MR, et al. Characterization and chemical synthesis of Cm39 (α-KTx 4.8): a scorpion toxin that inhibits voltage-gated K+ channel KV1.2 and small- and intermediate-conductance Ca2+-Activated K+ Channels KCa2.2 and KCa3.1. Toxins (Basel). 2023;15:41.
39. Naseem MU, Carcamo-Noriega E, Beltrán-Vidal J, et al. Cm28, a scorpion toxin having a unique primary structure, inhibits KV1.2 and KV1.3 with high affinity. J Gen Physiol. 2022;154:e202213146.
40. Viswanathan S, Prabhu C. Scorpion sting nephropathy. NDT Plus. 2011;4:376–82.
41. Dehghani R, Ghorbani A, Varzandeh M, Karami-Robati F. Toxicity mechanism of dangerous scorpion stings in Iran. J Arthropod Borne Dis. 2023;17:105–19.
42. Saidani C, Hammoudi-Triki D, Laraba-Djebari F, Taub M. In vitro studies with renal proximal tubule cells show direct cytotoxicity of Androctonus australis hector scorpion venom triggered by oxidative stress, caspase activation and apoptosis. Toxicon. 2016;120:29–37.
43. de Sousa Alves R, do Nascimento NRF, Barbosa PSF, et al. Renal effects and vascular reactivity induced by Tityus serrulatus venom. Toxicon. 2005;46:271–6.
44. Silva NA, Albuquerque CMR, Marinho AD, et al. Effects of Tityus stigmurus (Thorell 1876) (Scorpiones: Buthidae) venom in isolated perfused rat kidneys. An Acad Bras Cienc. 2016;88(Suppl 1):665–75.
45. Afifi SH, El-Kashef R, Seddek AS, Salem DA. Light and transmission electron microscopical changes associated with venom in rabbits. Macedonian Veter Rev. 2016;39:51–7.
46. Galíndez-Cerón JD, Jorge RJB, Chavez-Acosta MH, et al. Renal alterations induced by the venom of colombian scorpion Centruroides Margaritatus. Curr Top Med Chem. 2019;19:2049–57.
47. Salman MMA, Hammad S. Oxidative stress and some biochemical alterations due to scorpion (Leiurus quinquestriatus) crude venom in rats. Biomed Pharmacother. 2017;91:1017–21.
48. Saidani C, Béchohra L, Laraba-Djebari F, Hammoudi-Triki D. Kidney inflammation and tissue injury induced by scorpion venom: comparison with a nephrotoxic model. Toxin Rev. 2019;38:240–7.
49. de Oliveira NA, Cardoso SC, Barbosa DA, da Fonseca CD. Acute kidney injury caused by venomous animals: inflammatory mechanisms. J Venom Anim Toxins Incl Trop Dis. 2021;27:20200189.
50. Mendoza-Tobar LL, Meza-Cabrera IA, Sepúlveda-Arias JC, Guerrero-Vargas JA. Comparison of the Scorpionism caused by Centruroides margaritatus, Tityus pachyurus and Tityus n. sp. aff. metuendus Scorpion Venoms in Colombia. Toxins (Basel). 2021;13:757.
51. Kusirisin P, da Silva Junior GB, Sitprija V, Srisawat N. Acute kidney injury in the tropics. Nephrology (Carlton). 2023;28:5–20.
52. Cajado-Carvalho D, Kuniyoshi AK, Duzzi B, et al. Insights into the hypertensive effects of Tityus serrulatus scorpion venom: purification of an angiotensin-converting enzyme-like peptidase. Toxins (Basel). 2016;8:348.
53. Angsanakul J, Sitprija V. Scorpion venoms, kidney and potassium. Toxicon. 2013;73:81–7.
54. Cupo P. Clinical update on scorpion envenoming. Rev Soc Bras Med Trop. 2015;48:642–9.
55. Malhotra KK, Mirdehghan CM, Tandon HD. Acute renal failure following scorpion sting. Am J Trop Med Hyg. 1978;27:623–6.
56. Chadha JS, Leviav A. Hemolysis, renal failure, and local necrosis following scorpion sting. JAMA. 1979;241:1038.
57. Mocan H, Mocan MZ, Kaynar K. Haemolytic-uraemic syndrome following a scorpion sting. Nephrol Dial Transplant. 1998;13:2639–40.

58. Bahloul M, Ben Hmida M, Belhoul W, et al. Hemolytic-uremic syndrome secondary to scorpion envenomation (apropos of 2 cases). Nephrologie. 2004;25:49–51.
59. Krkic-Dautovic S, Begovic B. Acute renal insufficiency and toxic hepatitis following scorpions sting. Med Arh. 2007;61:123–4.
60. Valavi E, Ansari MJA. Hemolytic uremic syndrome following Hemiscorpius lepturus (scorpion) sting. Indian J Nephrol. 2008;18:166–8.
61. Valavi E, Ahmadzadeh A, Amoori P, Daneshgar A. High frequency of acquired ADAMTS13 deficiency after hemolysis in Hemiscorpius Lepturus (scorpion) stung children. Indian J Pediatr. 2014;81:665–9.
62. Ranaweera GG, Bavanthan V, Nazar ALM, Lokuhetty MDS. Acute renal insufficiency after scorpion sting. Ceylon Med J. 2015;60:31–2.
63. Naqvi R. Scorpion sting and acute kidney injury: case series from Pakistan. BJMMR. 2015;9:1–6.
64. Albuquerque PLMM, Magalhaes K do N, Sales T de C, et al. Acute kidney injury and pancreatitis due to scorpion sting: case report and literature review. Rev Inst Med Trop Sao Paulo. 2018;60:e30.
65. LoVecchio F. Scorpion envenomation causing skin necrosis, hemolysis, DIC, and acute kidney injury (Middle East). UpToDate. 2022;
66. Dizaji R, Sharafi A, Pourahmad J, et al. Induction of two independent immunological cell death signaling following hemoglobinuria -induced acute kidney injury: in vivo study. Toxicon. 2019;163:23–31.
67. Dizaji R, Sharafi A, Pourahmad J, et al. The effects of Hemiscorpius lepturus induced-acute kidney injury on PGC-1α gene expression: from induction to suppression in mice. Toxicon. 2020;174:57–63.
68. Gmar-Bouraoui S, Aloui S, Ben Dhia N, et al. Scorpion sting and acute interstitial nephropathy: apropos of 1 case. Med Trop (Mars). 2000;60:305–6.
69. Boju SL, Mogili HKR, Ram R, Vishnubotla SK. Nephrotic syndrome after scorpion sting. CEN Case Rep. 2016;5:83–6.
70. Sagheb MM, Sharifian M, Moini M, Sharifian AH. Scorpion bite prevalence and complications: report from a referral centre in southern Iran. Trop Dr. 2012;42:90–1.
71. Valavi E, Amuri P, Ahmadzadeh A, et al. Acute kidney injury in Hemiscorpius lepturus scorpion stung children: risk factors and clinical features. Saudi J Kidney Dis Transpl. 2016;27:936–41.
72. Mégarbane B, Abroug F, Soulaymani R. Scorpion envenomation. N Engl J Med. 2014;371:1557–8.
73. Amin R, Faiz A. Scorpion sting and envenomation. En: Clinical toxinology in Asia Pacific and Africa. Dordrecht: Springer Netherlands; 2015. p. 455–482.
74. Godoy DA, Badenes R, Seifi S, et al. Neurological and systemic manifestations of severe scorpion envenomation. Cureus. 2021;13:e14715.
75. Ayerbe González S, Rodríguez Buitrago JR. Accidente Arácnido. Guías para el manejo de Urgencias Toxicológicas. Bogotá: Ministerio de Protección Social; 2008. p. 290–3.
76. D'Suze G, Corzo Burguete GA, Paniagua Solís JF, editores. Emergencias por animales ponzoñosos de las Américas. Mexico: Instituto Bioclon, CONACYT; 2011.
77. Kluz-Zawadzka J, Hartman-Ksycińska A, Lewandowski B. Emergent management of scorpion sting. Przegl Epidemiol. 2014;68:685–8.
78. Fonger GC, Hakkinen PJ, Publicker S. Venoms and antivenoms: north American poisonous scorpion, snake, and spider information is now in the National Library of Medicine's Hazardous Substances Data Bank. Clin Toxicol (Phila). 2015;53:74.
79. Ozkan O, Yağmur EA. Neutralization capacity of monovalant antivenom against existing lethal scorpions in the Turkish Scorpiofauna. Iran J Pharm Res. 2017;16:653–60.
80. Martin-Eauclaire M-F, Adi-Bessalem S, Hammoudi-Triki D, et al. Serotherapy against voltage-gated Sodium Channel-targeting αToxins from Androctonus scorpion venom. Toxins (Basel). 2019;11:63.
81. Shayesteh AA, Zamiri N, Peymani P, et al. A novel management method for disseminated intravascular coagulation like syndrome after a sting of Hemiscorpius lepturus: a case series. Trop Biomed. 2011;28:518–23.
82. Mostafazadeh B, Gorbani A, Mogaddaspour M, et al. The effect of plasmapheresis on treating disseminated intravascular coagulation (DIC) caused by a Hemiscorpius lepturus (Gadim) sting. Clin Toxicol (Phila). 2017;55:902–7.
83. Góngora-Ortega J, Serna-Vela Francisco J, Gutiérrez-Mendoza I, et al. Prevalencia de enfermedad renal crónica en niños de Aguascalientes. México Salud Publica Mex. 2008;50:436–7.
84. Gutiérrez-Mendoza I, Serna-Vela FJ, Góngora-Ortega J, et al. Picadura de alacrán y su relación con la enfermedad renal crónica infantil. Salud Pública Mex. 2011;53:107.
85. Robitaille P, Clermont M-J, Mérouani A, et al. Hemolytic uremic syndrome: late renal injury and changing incidence-a single centre experience in Canada. Scientifica (Cairo). 2012;2012:341860.
86. Ding J, Chua P-J, Bay B-H, Gopalakrishnakone P. Scorpion venoms as a potential source of novel cancer therapeutic compounds. Exp Biol Med (Maywood). 2014;239:387–93.
87. Bhavya J, Francois NN, More VS, More SS. Scorpion toxin polyptides as therapeutic agents: an overview. Protein Pept Lett. 2016;23:848–59.
88. Ayala Villamil ML. Veneno de escorpión colombiano podría eliminar células cancerígenas. UN Periodico. 198.a ed. abril de 2016;12–3.
89. Santussi WM, Bordon KCF, Rodrigues Alves APN, et al. Antifungal activity against filamentous fungi of Ts1, a multifunctional toxin from Tityus serrulatus scorpion venom. Front Microbiol. 2017;8:984.
90. Tran TV, Hoang AN, Nguyen TTT, et al. Anticoagulant activity of low-molecular weight compounds from Heterometrus laoticus scorpion venom. Toxins (Basel). 2017;9:343.

91. Perumal Samy R, Stiles BG, Franco OL, et al. Animal venoms as antimicrobial agents. Biochem Pharmacol. 2017;134:127–38.
92. Wan T, Li L, Zhu Z, et al. Scorpion venom active polypeptide may be a new external drug of diabetic ulcer. Evid Based Complement Alternat Med. 2017;2017:5161565.
93. Khamessi O, Ben Mabrouk H, ElFessi-Magouri R, Kharrat R. RK1, the first very short peptide from Buthus occitanus tunetanus inhibits tumor cell migration, proliferation and angiogenesis. Biochem Biophys Res Commun. 2018;499:1–7.
94. Uzair B, Bint-E-Irshad S, Khan BA, et al. Scorpion venom peptides as a potential source for human drug candidates. Protein Pept Lett. 2018;25:702–8.
95. Dueñas-Cuellar RA, Santana CJC, Magalhães ACM, et al. Scorpion toxins and ion channels: potential applications in cancer therapy. Toxins (Basel). 2020;12:326.
96. Mendes LC, Viana GMM, Nencioni ALA, et al. Scorpion peptides and ion channels: an insightful review of mechanisms and drug development. Toxins (Basel). 2023;15:238.

10 Spider Bite Nephropathy

Edgar Sanclemente-Paz

Spiders of the *Loxosceles* species, in addition to producing dermonecrosis lesions, can present systemic manifestations such as hemorrhages, hemolysis, and rhabdomyolysis that can lead to acute kidney injury (AKI) [1–9].

10.1 Epidemiology

In South America, specifically in Brazil, three types of *Loxosceles* have been described as important in the poisoning of humans—*L. intermedia*, *L. gaucho*, and *L. laeta*—and in North America, *L. reclusa* is found (Fig. 10.1).

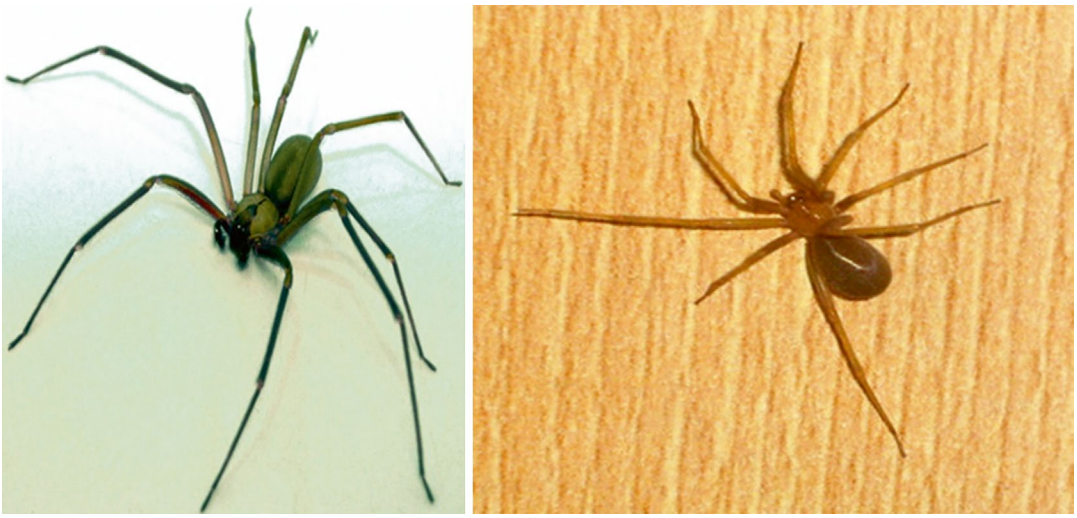


Fig. 10.1 Spiders. *Loxosceles reclusa* and *Loxosceles laeta*. (Reproduced from Wikipedia)

E. Sanclemente-Paz (✉)
Department of Internal Medicine,
Faculty of Medicine, University of Cauca,
Popayán, Cauca, Colombia
e-mail: esanclemente@imbanaco.com.co

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_10

10.2 Venom Composition

Spider venom is a mixture of toxins such as phospholipase D, hyaluronidases, serine proteases, protease inhibitory factors, histamine-releasing factors, astacin-like metalloproteinases, and cystine-knot peptide (CKP) and neurotoxins [10–15].

Nephrotoxicity.

Experimentally, venom inoculation in mice showed glomerular edema and tubular necrosis. In in vitro studies with MDCK cells, the venom produced alterations with vacuole formation and cell apoptosis. In another study in rats, venom administration injured proximal tubule cells.

Glomerular edema, basal membrane lesions, and tubular necrosis were observed when phospholipase D from the venom of the spider *Loxosceles* genus was administered to mice [16–19].

Sphingomyelinase D (SMase D) present in the venom is apparently responsible for local and systemic manifestations, producing cell apoptosis at the renal level. It also produces the activation of an endogenous metalloproteinase, which attacks glycophorins, making red blood cells more susceptible to lysis by the complement, this being the proposed mechanism for the production of hemolysis. Other enzymes such as hyaluronidase are responsible for the extension of the action of the venom and the development of the inflammatory phenomenon with edema and ischemia leading to rhabdomyolysis. High concentrations of interleukin-6 and tumor necrosis factor alpha have been detected as mediators of the inflammatory phenomenon. Elevated levels of D-dimer are suggestive of endothelial dysfunction and intravascular thrombin generation. An immunological component linked to the injury caused by spider venom has been proposed [10, 20, 21] (Fig. 10.2).

The factors associated with the development of AKI due to pigmented nephropathy with acute tubular necrosis, caused by spider venom, are

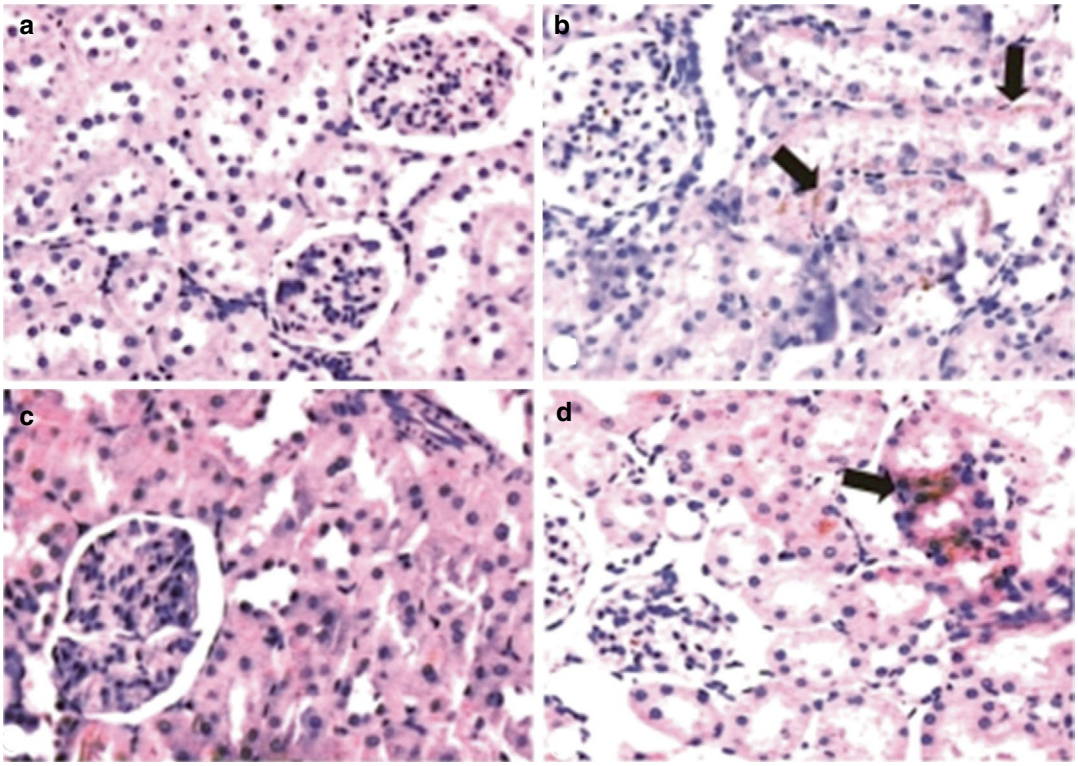


Fig. 10.2 Spider-induced kidney injury (*Loxosceles gaucho*, experimental). (**a** and **c**) Control. (**b** and **d**) Tubular necrosis (myoglobin stain). (Reproduced with permission from Lucato et al. Plos Negl Trop Med 2011; 5(5): e1182)

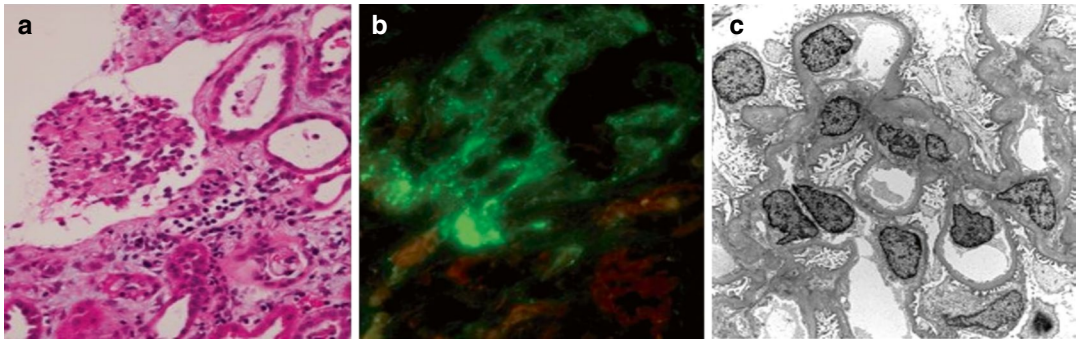


Fig. 10.3 Spider-induced kidney injury (brown spider, *Loxosceles reclusa*). (**a**) Glomerular and tubular injury. (**b**) C3 deposits in mesangium and capillary walls. (**c**) Podocyte injury. (Reproduced with permission from Amwar et al. Clin Kidney J 2013; 6(6): 609–612)

hemodynamic disorders accompanied by hypotension and shock, as well as alteration of microcirculation, hemolysis, rhabdomyolysis, thrombocytopenia, and a direct tubular and glomerular nephrotoxic action with immune deposits (complement and IgG), as well as alteration of selective permeability inducing proteinuria. Renal lesions are particularly severe in children, in whom hemolytic anemia is observed in half of the cases, rhabdomyolysis in 27%, and acute kidney injury in 12%. AKI secondary to spider envenomation according to studies in Brazil is between 3.3% and 6.4%. In the retrospective study carried out in the USA in patients with severe loxoscelism due to *L. reclusa*, a mortality rate of 3.5% was observed [22–30].

In an epidemiological study in Chile in patients with bites from the spider *Loxosceles laeta*, hematuria and hemoglobinuria were constant findings [2].

A study carried out in the northwestern region of Brazil in 42 cases of loxoscelism revealed the presence of acute kidney injury in 11.9% of cases [28].

Another study in the same country between 2010 and 2015 revealed that 13.3% of patients with spider bites developed acute kidney injury [31].

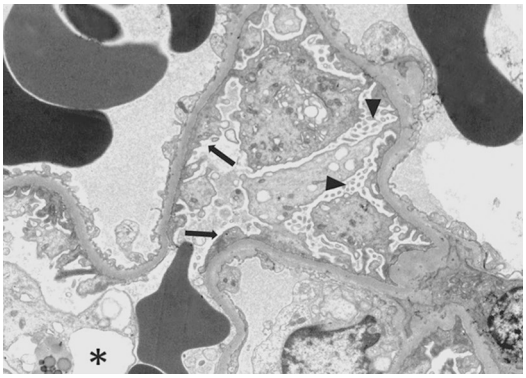


Fig. 10.4 Spider-induced kidney injury. Minimal change disease, podocyte fusion. (Reproduced with permission from Mendez G et al. Clin Kidney J 2017; 10(2): 229–232)

In a study carried out in a third-level hospital in Mexico, in patients with systemic loxoscelism, 67% presented renal complications [32].

Glomerular involvement with mesangial proliferation and immune complex (C3) deposits in the mesangium and vessels, as well as podocyte injury [33], has been described (Fig. 10.3).

A case of minimal change disease with nephrotic syndrome secondary to spider bites has been reported [34] (Fig. 10.4).

10.3 Treatment

Although there are doubts about the efficacy of antivenom in the treatment of acute renal failure due to the bite of spiders of the genus *Loxosceles*, some groups of researchers consider it an effective therapy in the management of these cases. Currently, drugs are being developed that bind to the catalytic site of the enzyme phospholipase D, interacting with important residues (His 12 and His 47) and the cofactor Mg++ [3, 7, 12, 19, 22, 23, 33, 35–44].

Recent studies indicate that tetracycline can prevent cell death caused by sphingomyelinase D and inhibits the synthesis and secretion of metalloproteinases (MMP-2 and MMP-9), which could be useful in the treatment of loxoscelism [45].

10.4 Venom Applications

Significant insecticidal activity has been observed in the recombinant peptide knottin from *Loxosceles intermedia* venom by its action on potassium ion channels and receptors of the insect nervous system [46–48]. Antibiotic and anticancer properties have been found in the venom of some types of spiders [49–51].

The families Lycosidae and Theraphosidae (tarantulas) and the genus *Latrodectus* (black widow) mainly produce neurotoxins (α-latrotoxin). However, only one case of AKI secondary to the bite of *Latrodectus*-type spiders is described [1, 36, 37, 51–53].

10.5 Take-Home Message

- Climate change has led to a greater proliferation of different types of poisonous spiders.
- Kidney involvement is common in loxoscelism and is more severe in children.
- Necessary precautions should be taken to avoid the bite of these insects and their complications.

References

1. de Roodt AR, Lanari LC, Laskowicz RD, et al. Toxicity of the venom of Latrodectus (Araneae: Theridiidae) spiders from different regions of Argentina and neutralization by therapeutic antivenoms. Toxicon. 2017;130:63–72.
2. Schenone H, Saavedra T, Rojas A, Villarroel F. Loxoscelismo en Chile: estudios epidemiológicos, clínicos y experimentales. Rev Inst Med Trop Sao Paulo. 1989;31:403–15.
3. Zambrano FA, González CJ, Callejas GG. Desenlace fatal por loxoscelismo cutáneo visceral: Report of one case. Rev Med Chile. 2005;133:219–23.
4. Cabrerizo S, Docampo PC, Cari C, et al. Loxoscelismo: epidemiología y clínica de una patología endémica en el país. Arch Argent Pediatr. 2009;107:152–9.
5. McDade J, Aygun B, Ware RE. Brown recluse spider (Loxosceles reclusa) envenomation leading to acute hemolytic anemia in six adolescents. J Pediatr. 2010;156:155–7.
6. Sánchez-Olivas MA, Valencia-Zavala MP, Sánchez-Olivas JA, et al. Loxoscelismo cutáneo necrótico. Informe de un caso. Rev Alergia Mex. 2011;58:171–6.
7. Hubbard JJ, James LP. Complications and outcomes of brown recluse spider bites in children. Clin Pediatr (Phila). 2011;50:252–8.
8. Isbister GK, Fan HW. Spider bite. Lancet. 2011;378:2039–47.
9. Vetter RS, Swanson DL. Bites of recluse spiders. UpToDate; 2024.
10. Abdulkader RCRM, Barbaro KC, Barros EJG, Burdmann EA. Nephrotoxicity of insect and spider venoms in Latin America. Semin Nephrol. 2008;28:373–82.
11. Gremski LH, Trevisan-Silva D, Ferrer VP, et al. Recent advances in the understanding of brown spider venoms: from the biology of spiders to the molecular mechanisms of toxins. Toxicon. 2014;83:91–120.
12. Chaves-Moreira D, Senff-Ribeiro A, Wille ACM, et al. Highlights in the knowledge of brown spider toxins. J Venom Anim Toxins Incl Trop Dis. 2017;23:6.
13. Masood R, Ullah K, Ali H, et al. Spider's venom phospholipases D: a structural review. Int J Biol Macromol. 2018;107:1054–65.
14. Gremski LH, da Justa HC, da Silva TP, et al. Forty years of the description of bsrown spider venom phospholipases-D. Toxins (Basel). 2020;12:164.
15. Gremski LH, Matsubara FH, da Justa HC, et al. Brown spider venom toxins: what are the functions of astacins, serine proteases, hyaluronidases, allergens, TCTP, serpins and knottins? J Venom Anim Toxins Incl Trop Dis. 2021;27:e20200188.
16. Luciano MN, da Silva PH, Chaim OM, et al. Experimental evidence for a direct cytotoxicity of Loxosceles intermedia (brown spider) venom in renal tissue. J Histochem Cytochem. 2004;52:455–67.

17. Chaim OM, Sade YB, da Silveira RB, et al. Brown spider dermonecrotic toxin directly induces nephrotoxicity. Toxicol Appl Pharmacol. 2006;211:64–77.
18. Kusma J, Chaim OM, Wille ACM, et al. Nephrotoxicity caused by brown spider venom phospholipase-D (dermonecrotic toxin) depends on catalytic activity. Biochimie. 2008;90:1722–36.
19. Malaque CMS, Santoro ML, Cardoso JLC, et al. Clinical picture and laboratorial evaluation in human Loxoscelism. Toxicon. 2011;58:664–71.
20. Lucato RV, Abdulkader RCRM, Barbaro KC, et al. Loxosceles gaucho venom-induced acute kidney injury--in vivo and in vitro studies. PLoS Negl Trop Dis 2011;5:e1182.
21. Pichardo-Rodríguez R. Injuria renal aguda en Loxoscelismo, aspectos inmuno-histopatológicos. RFMH. 2018;18:103–4.
22. González TC, Saffie IA, Fardella BC, Contreras SA. Insuficiencia renal aguda en Loxocelismo cutaneo-visceral: 11 casos. Rev Med Chile. 1986;114:1155–9.
23. Sezerino UM, Zannin M, Coelho LK, et al. A clinical and epidemiological study of Loxosceles spider envenoming in Santa Catarina, Brazil. Trans R Soc Trop Med Hyg. 1998;92:546–8.
24. de França FOS, Barbaro KC, de Abdulkader RCRM. Rhabdomyolysis in presumed viscerocutaneous Loxoscelism: report of two cases. Trans R Soc Trop Med Hyg. 2002;96:287–90.
25. Alfaro FV, Dotto B, Sesin AM, et al. Loxoscelismo cutáneo-viscero-hemolítico confallo renal agudo. Rev Fac Cien Med Univ Nac Cordoba. 2008;65:142–6.
26. Cristina de Oliveira-Lima K, Farsky SHP, Lopes PH, et al. Microcirculation abnormalities provoked by Loxosceles spiders' envenomation. Toxicon. 2016;116:35–42.
27. Pezzi M, Giglio AM, Scozzafava A, et al. Spider bite: a rare case of acute necrotic arachnidism with rapid and fatal evolution. Case Rep Emerg Med. 2016;2016:7640789.
28. Oliveira Filho AM, Daher EF, Albuquerque PL, et al. Acute kidney injury caused by snakebites in patients admitted to a reference toxicological assistance center in Northeast Brazil. Nephrol Dial Transpl. 2016;31(1):i150.
29. Robinson JR, Kennedy VE, Doss Y, et al. Defining the complex phenotype of severe systemic Loxoscelism using a large electronic health record cohort. PLoS One. 2017;12:e0174941.
30. Ma B, Xi Z, Li J, et al. Vasodilator and hypotensive effects of the spider peptide Lycosin-I in vitro and in vivo. Peptides. 2018;99:108–14.
31. Albuquerque PLMM, Tessarolo LD, Menezes FH, et al. Acute kidney injury due to systemic Loxoscelism: a cross-sectional study in Northeast Brazil. Rev Soc Bras Med Trop. 2018;51:695–9.
32. Moranchel-García L, Pineda-Galindo LF, Casarrubias-Ramírez M, et al. Evolución clínica de pacientes con loxoscelismo sistémico y dermonecrótico en un hospital de tercer nivel. Medicina interna de México. 2017;33:18–27.
33. Anwar S, Torosyan R, Ginsberg C, et al. Clinicopathological course of acute kidney injury following brown recluse (Loxosceles reclusa) envenomation. Clin Kidney J. 2013;6:609–12.
34. Méndez GP, Enos D, Moreira JL, et al. Nephrotic syndrome due to minimal change disease secondary to spider bite: clinico-pathological case of a non-described complication of latrodectism. Clin Kidney J. 2017;10:229–32.
35. Ayerbe González S, Rodríguez Buitrago JR. Accidente Arácnido. Guías para el manejo de Urgencias Toxicológicas. Bogotá: Ministerio de Protección Social; 2008. p. 290–3.
36. Peterson ME. Black widow spider envenomation. Clin Tech Small Anim Pract. 2006;21:187–90.
37. Peterson ME. Brown spider envenomation. Clin Tech Small Anim Pract. 2006;21:191–3.
38. Pauli I, Puka J, Gubert IC, et al. The efficacy of antivenom in loxoscelism treatment. Toxicon. 2006;48:123–37.
39. de Souza AL, Malaque CM, Sztajnbok J, et al. Loxosceles venom-induced cytokine activation, hemolysis, and acute kidney injury. Toxicon. 2008;51:151–6.
40. Rosen JL, Dumitru JK, Langley EW, et al. Emergency department death from systemic loxoscelism. Ann Emerg Med. 2012;60:439–41.
41. Golay V, Desai A, Hossain A, et al. Acute kidney injury with pigment nephropathy following spider bite: a rarely reported entity in India. Ren Fail. 2013;35:538–40.
42. Nag A, Datta J, Das A, et al. Acute kidney injury and dermonecrosis after Loxosceles reclusa envenomation. Indian J Nephrol. 2014;24:246–8.
43. Tavares FL, Peichoto ME, Marcelino JR, et al. Platelet participation in the pathogenesis of dermonecrosis induced by Loxosceles gaucho venom. Hum Exp Toxicol. 2016;35:666–76.
44. Maguiña Vargas C, Figueroa Vásquez V, Pulcha Ugarte R. Actualización sobre manejo de araneismo en Perú. Revista Medica Herediana. 2017;28:200–7.
45. Okamoto CK, van den Berg CW, Masashi M, et al. Tetracycline reduces kidney damage induced by Loxosceles spider venom. Toxins (Basel). 2017;9:90.
46. Matsubara FH, Meissner GO, Herzig V, et al. Insecticidal activity of a recombinant knottin peptide from Loxosceles intermedia venom and recognition of these peptides as a conserved family in the genus. Insect Mol Biol. 2017;26:25–34.
47. Windley MJ, Vetter I, Lewis RJ, Nicholson GM. Lethal effects of an insecticidal spider venom peptide involve positive allosteric modulation of insect nicotinic acetylcholine receptors. Neuropharmacology. 2017;127:224–42.
48. Jiménez-Vargas JM, Possani LD, Luna-Ramírez K. Arthropod toxins acting on neuronal potassium channels. Neuropharmacology. 2017;127:139–60.

49. Ferreira FRB, da Silva PM, Soares T, et al. Evaluation of antimicrobial, cytotoxic, and hemolytic activities from venom of the spider Lasiodora sp. Toxicon. 2016;122:119–26.
50. Wilson D, Boyle GM, McIntyre L, et al. The aromatic head group of spider toxin polyamines influences toxicity to cancer cells. Toxins (Basel). 2017;9:346.
51. Karcioglu O, Gumustekin M, Tuncok Y, Celik A. Acute renal failure following latrodectism. Vet Hum Toxicol. 2001;43:161–3.
52. Yan S, Wang X. Recent advances in research on widow spider venoms and toxins. Toxins (Basel). 2015;7:5055–67.
53. Rueda A, Realpe E, Uribe A. Toxicity evaluation and initial characterization of the venom of a Colombian Latrodectus sp. Toxicon. 2017;125:53–8.

11 Kidney Injuries Secondary to Ant Bites

Edgar Sanclemente-Paz

11.1 Epidemiology

Ants are insects of the *Hymenoptera* family of the *Formicidae* family and the *Solenopsis* genus. Red or fire ants (*Solenopsis invicta*), which are found in North and Central America and the Caribbean.

11.2 Venom Composition

Formic acid present in the venom of all types of ants is the cause of the burning and pain of the sting and also aims to inhibit the growth of pathogenic fungi in the colonies [1].

Their venom is also composed of the alkaloid piperidine and allergenic proteins, capable of inducing allergic and anaphylaxis phenomena. It also contains phospholipase A2, myotoxins, and neurotoxins. This type of venom is cytotoxic, neurotoxic, and hemolytic, increases the coagulation phenomenon, and predisposes to a state of hypercoagulability with platelet activation and endothelial damage, developing a hemolytic uremic syndrome which can induce acute kidney injury [2–10] (Fig. 11.1).

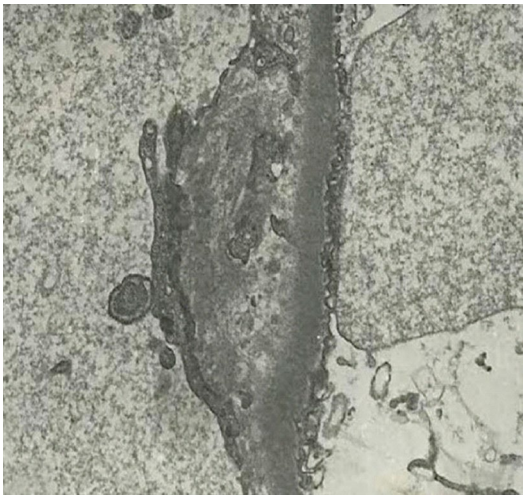


Fig. 11.1 Hemolytic-uremic syndrome associated with ant bite—subendothelial widening, double contour of basement membrane. (Reproduced, with permission from Lee et al. [5])

Other venom components such as solenopsins act on the neuromuscular junction, block the ATP-dependent Na+/K+ pump, and inhibit nitric oxide synthases [11].

The presence of atrial natriuretic peptide in the venom of red or fire ants (*Solenopsis invicta*), a hormone that regulates water and sodium balance and blood pressure, stimulating Na + excretion and producing vasodilation [10], has been demonstrated.

E. Sanclemente-Paz (✉)
Department of Internal Medicine,
Faculty of Medicine, University of Cauca,
Popayán, Cauca, Colombia
e-mail: esanclemente@imbanaco.com.co

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_11

11.3 Nephrotoxicity

A case has been reported of a woman found unconscious in shock with multiple fire ant stings, who developed disseminated vascular coagulation and AKI [12]. A case of rhabdomyolysis secondary to multiple fire ant stings is described, and another case with nephrotic syndrome associated with the venom of these insects [13–15]. A case of oliguric AKI secondary to multiple ant stings has been described [16]. Two cases of acute kidney injury secondary to stings by ants of the *Pseudomyrmex* species of the palo santo tree are known [17] (Fig. 11.2).

Cases of tubular necrosis with AKI have been described in dogs with multiple ant bites [18].

Fig. 11.2 Acute kidney injury due to ant bites (*Pseudomyrmex* spp.). (Reproduced, with permission, from Torres et al. [17])

11.4 Venom Applications

Experimental studies in rats have shown that alkaloids and nonpeptide compounds contained in Chinese black ants (*Polyrhachis dives*) have anti-inflammatory and protective properties on mesangial cells [19].

Ant venom, due to its alkaloids piperidine, piperidene and pyridine, is attributed with antifungal, antimicrobial, antiprotozoal, and insecticidal properties. Its possible use as a bioinsecticide has been advocated [1, 20–23].

New molecules derived from ant venom are currently being investigated in the treatment of cancer due to their angiogenic activity [24, 25].

11.5 Take-Home Message

- Ant bites can cause allergies and anaphylaxis.
- The toxins in the venom can eventually cause acute kidney injury.
- Measures must be implemented to prevent these bites and their complications, especially in children and the elderly.

References

1. Tragust S, Mitteregger B, Barone V, et al. Ants disinfect fungus-exposed brood by oral uptake and spread of their poison. Curr Biol. 2013;23:76–82.
2. Prahlow JA, Barnard JJ. Fatal anaphylaxis due to fire ant stings. Am J Forensic Med Pathol. 1998;19:137–42.
3. More DR, Kohlmeier RE, Hoffman DR. Fatal anaphylaxis to indoor native fire ant stings in an infant. Am J Forensic Med Pathol. 2008;29:62–3.
4. Cochran J, McSwain SD, Evans M, et al. Anaphylaxis and delayed hymenoptera in a child with fire ant envenomation. Am J Emerg Med. 2013;31(632):e1–3.
5. Lee Y-C, Wang J-S, Shiang J-C, et al. Haemolytic uremic syndrome following fire ant bites. BMC Nephrol. 2014;15:5.
6. Ralston JP, Rapini RP. Fire ant bites: practice essentials, background, pathophysiology. Medscape; 2022.
7. Al-Tamimi J, Alhazza IM, Al-Khalifa M, et al. Potential effects of samsum ant, Brachyponera sennaarensis, venom on TNF-α/NF-κB mediated inflammation in CCL4-toxicity in vivo. Lipids Health Dis. 2016;15:198.
8. Touchard A, Aili SR, Fox EGP, et al. The biochemical toxin arsenal from ant venoms. Toxins (Basel). 2016;8:30.
9. de Shazo RD, Goddard J, Kemp SF, Quinn JM. Stings of imported fire ants: clinical manifestations, diagnosis, and treatment. UpToDate; 2023.
10. Chen J. Chemistry and functions of imported fire ant venom. Toxins (Basel). 2023;15:489.
11. Pessoa WFB, Silva LCC, de Oliveira DL, et al. Analysis of protein composition and bioactivity of Neoponera villosa venom (Hymenoptera: Formicidae). Int J Mol Sci. 2016;17:513.
12. Bernaba M, Power E, Campion J, Gotzek D, Schmidt JO, Klotz SA. Unconscious woman in shock and covered with ants pulled from an abandoned automobile. Am J Med. 2019;132:1239–41.
13. Koya S, Crenshaw D, Agarwal A. Rhabdomyolysis and acute renal failure after fire ant bites. J Gen Intern Med. 2007;22:145–7.
14. Swanson GP, Leveque JA. Nephrotic syndrome associated with ant bite. Tex Med. 1990;86:39–41.
15. Prasad A, Kumar R, Ramanan H, et al. Rhabdomyolysis due to multiple fire ant bites a case report. Asian Pac J Trop Dis. 2012;2:417–8.
16. Aayilliath KA, Geetha P. Ant bite causing acute oliguric renal failure: A case report. GJHSR. 2023;0:1–3.
17. Tórrez Salazar J, Tórrez Salazar JT, Taboada JE, et al. Insuficiencia renal aguda por picadura de hormigas del Palo Santo (Pseudomyrmex spp). Gaceta Médica Boliviana. 2007;30:50–3.
18. Abraham LA, Hinkley CJ, Tatarczuch L, Holloway SA. Acute renal failure following Bull ant mass envenomation in two dogs. Aust Vet J. 2004;82:43–7.
19. Tang J-J, Fang P, Xia H-L, et al. Constituents from the edible Chinese black ants (Polyrhachis dives) showing protective effect on rat mesangial cells and anti-inflammatory activity. Food Res Int. 2015;67:163–8.
20. Aili SR, Touchard A, Escoubas P, et al. Diversity of peptide toxins from stinging ant venoms. Toxicon. 2014;92:166–78.
21. Primon-Barros M, José Macedo A. Animal venom peptides: potential for new antimicrobial agents. Curr Top Med Chem. 2017;17:1119–56.
22. Fratini F, Cilia G, Turchi B, Felicioli A. Insects, arachnids and centipedes venom: a powerful weapon against bacteria. A literature review. Toxicon. 2017;130:91–103.
23. Xu G, Chen L. Biological activities and ecological significance of fire ant venom alkaloids. Toxins (Basel). 2023;15:439.
24. Vétillard A, Bouzid W. Ants: a chemical library of anticancer molecules. Biol Aujourdhui. 2016;210:119–25.
25. Al-Tamimi J, Semlali A, Hassan I, et al. Samsum ant venom exerts anticancer activity through immunomodulation in vitro and in vivo. Cancer Biother Radiopharm. 2018;33:65–73.

12 Kidney Injury Caused by Marine Toxins

Edgar Sanclemente-Paz

12.1 Epidemiology

Environmental changes have made toxins from marine animals more prominent in coastal regions and accumulate in fish and shellfish, which when consumed, can affect human health. Marine toxins have received little attention regarding their deleterious effects on the kidney, so there is very little literature on the subject [1–4].

Jellyfish are marine creatures with an almost transparent body with tentacle-like structures. Their sting, by discharging nematocytes, generally produces hives, but can cause serious injuries due to the ability of the venom to induce hemolysis [5] (Figs. 12.1 and 12.2).

The main species include the sea melena (*Cyanea capillata*), the Portuguese man-of-war (*Physalia physalis*), the sea nettle (*Chrysaora quinquecirrha*) and the box jellyfish (*Chironex fleckeri*, *Chiropsalmus quadrigatus*).

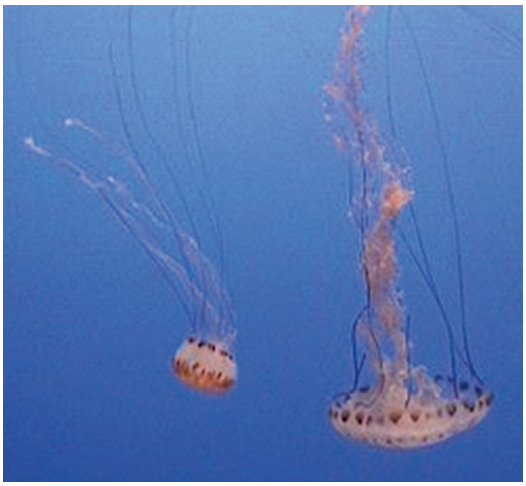


Fig. 12.1 Jellyfish. (Source: Wikipedia)

E. Sanclemente-Paz (✉)
Department of Internal Medicine,
Faculty of Medicine, University of Cauca,
Popayán, Cauca, Colombia
e-mail: esanclemente@imbanaco.com.co

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_12

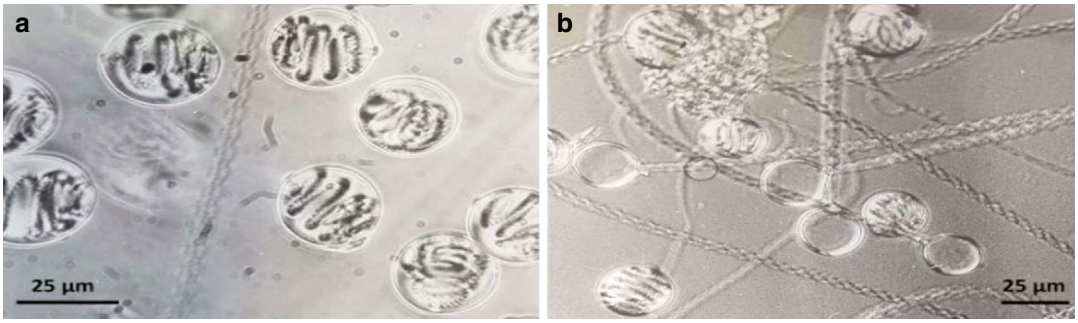


Fig. 12.2 Phase contrast microphotographs of (**a**) undischarged and (**b**) discharged holotrichous-isorhiza nematocysts isolated from *Pelagia noctiluca* (Cnidaria: *Scyphozoa*) oral arms. (Reproduced with permission from Remigante et al. [6])

12.2 Venom Composition and Nephrotoxicity

Marine toxins such as domoic acid, palytoxin, maitotoxin, and cniradian toxin are potentially nephrotoxic. Some inhibit the angiotensin I-converting enzyme. They also contain phospholipases A2 and metalloproteases that induce lipid peroxidation with the formation of reactive oxygen species, generating oxidative stress and producing proteolysis, rhabdomyolysis, and hemolysis. The AbTX1 toxin acts on K+ channels, and the peptides contained in the venoms activate Na + channels and also the voltage-dependent Ca++ channels, forming pores in the cell membrane that facilitate the entry of sodium and calcium, inducing the release of catecholamines, 6-hydroxytryptamine, prostaglandins and kinins, resulting in hemodynamic alterations [2, 7–20]. Domoic acid, produced by the plankton species *Pseudo-nitzschia*, is a potent neurotoxin which increases cytosolic Ca++ and causes cell death through the production of free radicals by the action of phospholipase 2 and caspase 3. This compound accumulates in the proximal tubule and causes tubular and endothelial damage. It has been observed to contaminate crustaceans and snails [20] (Fig. 12.3).

Palytoxin contaminates some fish and is produced by the dinoflagellate *Ostreopsis ovata*, which inhibits the Na + K+ ATPase enzyme and opens the Ca + and Na + channels, causing edema and apoptosis of the cell. The clinical picture presents with hypertension and may present rhabdomyolysis, hemolysis, hyperkalemia, and acute kidney injury. It contaminates some species of fish [21, 22].

Maitotoxin contaminates some fish and is produced by the dinoflagellate *Gambierdiscus toxicus*; it acts on the ion channels and the epithelial Ca++ channels, forming pores in the cell membrane, causing cell death with activation of the inflammatory phenomenon. The cnidarian toxin present in jellyfish venom acts on Na + and K+ channels, creating pores in the cell membrane that lead to cell death [23].

The membrane attack complex (Perforin) present in anemones causes complement activation, causing vascular, glomerular, and tubular damage, developing mesangiolysis, fibrin deposits in the glomeruli, and tubular necrosis. By generating pores in the cell membrane, apoptosis of the cells occurs, which is why, in addition to skin damage, acute kidney injury, and hemolytic uremic syndrome develop [24–26].

Toxins present in the classes of Anthosoas, Hidrosoas, Cubosoas, and Scyfosoas create pores in the cell membrane, affect ion transport through blocking of ion channels and produce an increase in cytosolic Na + and Ca++, which leads to cellular edema and loss of macromolecules and nutrients due to the formation of pores that end in mitochondrial dysfunction with apoptosis and cellular necrosis. In addition, they stimulate the formation of free radicals and produce hemolysis, rhabdomyolysis, and coagulation disorders

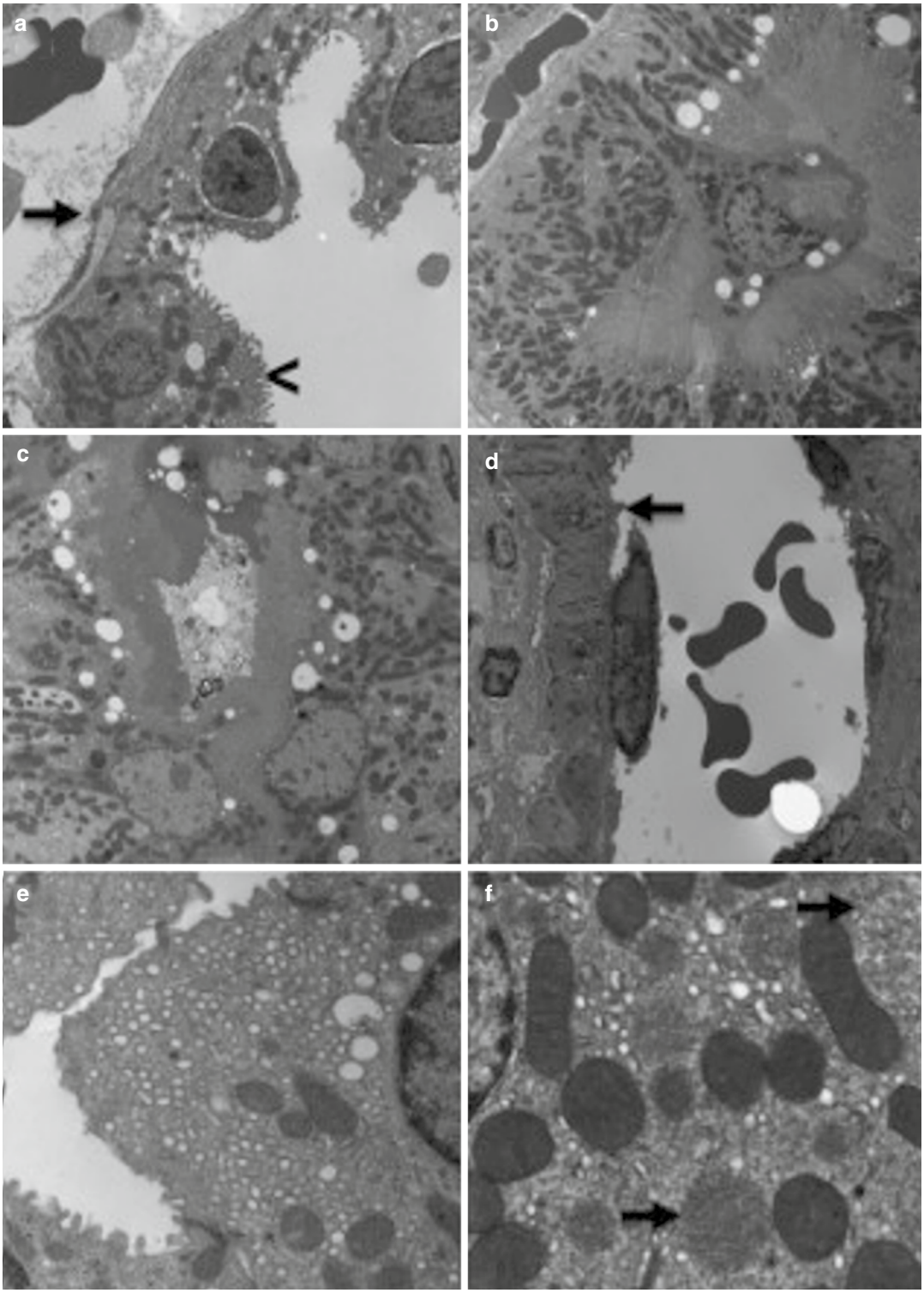


Fig. 12.3 Kidney injury induced by marine toxins, experimental study. (**a**) arrow: endothelial cell swelling; (**a**) arrowhead: epithelial cell vacuolization; (**b**) proximal tubule cell detachment; (**c**) luminal protenaceous material and cellular debris. Higher-magnification views more clearly showed (**d**) arrow: endothelial cell damage; (**e**) toxic vacuolization, and (**f**) arrows: mitochondrial swelling after DA administration. (Reproduced with permission from Funk et al. [19])

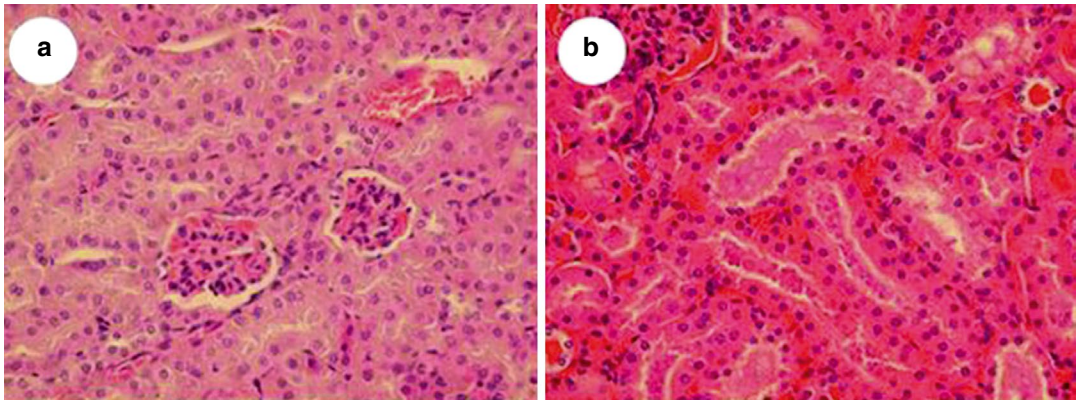


Fig. 12.4 Kidney injury by *Cnidaria*. Acute tubular necrosis (experimental, after the administration the *M. alcicornis* aqueous extract by intravenous route): (**a**) control kidney section, (**b**) kidney section of mice previously administered with the venom extract (with severe peritubular capillary congestion). (Reproduced with permission from Hernández-Matehuala et al. [11])

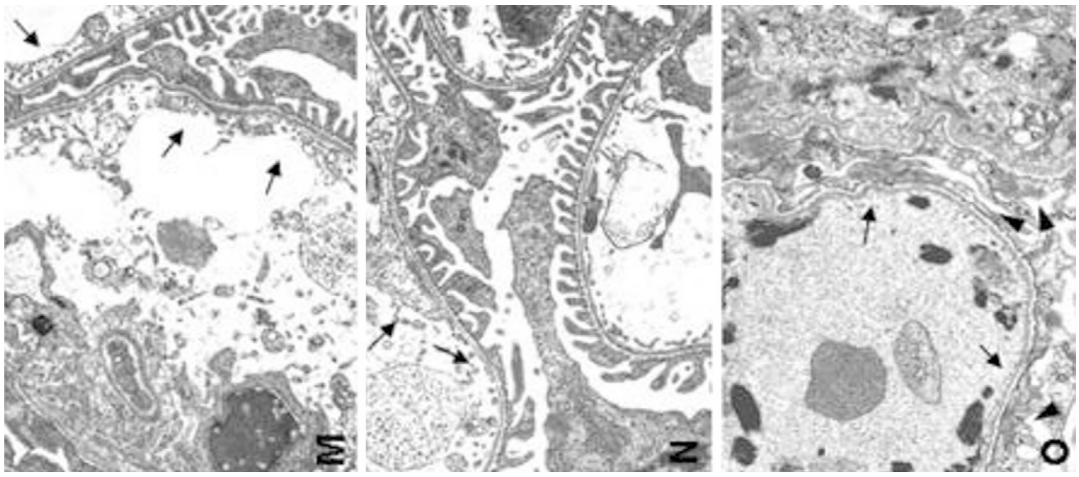


Fig. 12.5 Kidney injury induced by sea anemones. Glomerular endothelial injury. (Reproduced with permission from Mizuno et al. [47])

that can lead to disseminated intravascular coagulation. In addition to direct cytotoxicity, there is a vasoconstriction phenomenon with decreased renal blood flow that induces acute tubular necrosis [9, 18, 27–41] (Figs. 12.3 and 12.4).

There are several described cases of rhabdomyolysis and acute kidney injury with tubular necrosis and sometimes hemolytic uremic syndrome caused by jellyfish [42–47]. A case of nephrotic syndrome secondary to a jellyfish sting has been reported [48]. The PsTX-T toxin from the anemone *Phyllodiscus semoni* has experimentally produced glomerular injury by attacking the endothelium through complement activation in addition to tubular necrosis [49] (Fig. 12.5).

The toxin (PLA2) of a species of anemone (*Bunodosoma caissarum*), abundant in the southwest coast of Brazil, exhibits cytolytic, hemolytic, and neurocardiotoxic properties that can eventually cause shock and acute kidney injury [50].

The "Irukandji" syndrome has been described in Australia, Florida, and the Caribbean,

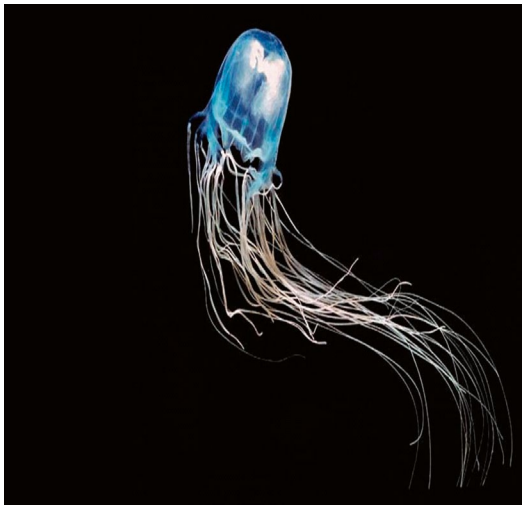


Fig. 12.6 Jellyfish *Carukia barnesi*. (Wikipedia)

described by Dr. Hugo Flecker in 1952 who named it after an indigenous tribe of Australia and later Dr. Jack Barnes proved that it was produced by the venom of the jellyfish *Carukia barnesi* and *shinju* and consists of hypertensive crisis due to the massive release of catecholamines, acute heart failure, and pulmonary edema, anaphylactic reaction due to the release of histamine and cytokines [51–55] (Fig. 12.6).

Treatment consists of the administration of intravenous magnesium sulfate, antihypertensive medications, antihistamines, and opiates. In case of acute kidney injury due to rhabdomyolysis, renal replacement therapy may be necessary [15, 55, 56].

12.3 Venom Application

The venoms of marine species have become important tools for the study of cellular physiology and the discovery of new molecules that are very useful in the treatment of some pathological conditions. Kunitz-type peptides inhibit different proteases and modulate ion channels and their receptors, demonstrating analgesic, anti-inflammatory, and antihistamine properties. Peptides isolated from some jellyfish exhibit inhibitory power of the angiotensin I-converting enzyme [12, 32, 57–61].

Thanks to their cytotoxic and cytolytic action, cnidarian toxin and other venoms from anemonas, due to their modulating action on the immune system and their action on the oncogenic potassium channel (Kv10.1), could have therapeutic applications against cancer. These venoms have also been found to have anti-inflammatory, antibiotic, and antifungal properties [62–65].

12.4 Take-Home Message

- Caution should be taken when coming into contact with marine species such as jellyfish and others, due to severe anaphylactic reactions.
- It is important to have a first aid kit with adrenaline, steroids, and antihistamines available for cases of acute anaphylaxis.
- Children and adults with comorbidities may be more susceptible to these marine toxins, so contact with these species should be avoided.

References

1. Vera KC, Kolbach RM, Zegpi TMS, et al. Picaduras de medusas: actualización. Rev méd Chile. 2004;132 https://doi.org/10.4067/S0034-98872004000200014.
2. Sitprija V, Sitprija S. Renal injury induced by marine toxins: role of ion channels. Int J Nephrol Ther. 2016;2:001–6.
3. Knittel PS, Long PF, Brammall L, et al. Characterising the enzymatic profile of crude tentacle extracts from the South Atlantic jellyfish Olindias sambaquiensis (Cnidaria: Hydrozoa). Toxicon. 2016;119:1–7.
4. Hornbeak KB, Auerbach PS. Marine envenomation. Emerg Med Clin North Am. 2017;35:321–37.
5. Burnett JW, Calton GJ. Jellyfish envenomation syndromes updated. Ann Emerg Med. 1987;16:1000–5.
6. Remigante A, Costa R, Morabito R, et al. Impact of scyphozoan venoms on human health and current first aid options for stings. Toxins (Basel). 2018;10:133.
7. Tibballs J, Yanagihara AA, Turner HC, Winkel K. Immunological and toxinological responses to jellyfish stings. Inflamm Allergy Drug Targets. 2011;10:438–46.
8. Frazão B, Vasconcelos V, Antunes A. Sea anemone (Cnidaria, Anthozoa, Actiniaria) toxins: an overview. Mar Drugs. 2012;10:1812–51.
9. Wang B, Zhang L, Zheng J, et al. Multiple organ dysfunction: a delayed envenomation syndrome caused

by tentacle extract from the jellyfish Cyanea capillata. Toxicon. 2013;61:54–61.
10. Chakrabarty D, Rastogi A. Hemotoxic activity of jellyfish venom. In: Clinical toxinology in Asia Pacific and Africa. Dordrecht: Springer Netherlands; 2015. p. 539–52.
11. Hernández-Matehuala R, Rojas-Molina A, Vuelvas-Solórzano AA, et al. Cytolytic and systemic toxic effects induced by the aqueous extract of the fire coral Millepora alcicornis collected in the Mexican Caribbean and detection of two types of cytolisins. J Venom Anim Toxins Incl Trop Dis. 2015;21:36.
12. So PBT, Rubio P, Lirio S, et al. In vitro angiotensin I converting enzyme inhibition by a peptide isolated from Chiropsalmus quadrigatus Haeckel (box jellyfish) venom hydrolysate. Toxicon. 2016;119:77–83.
13. Madio B, Undheim EAB, King GF. Revisiting venom of the sea anemone Stichodactyla haddoni: omics techniques reveal the complete toxin arsenal of a well-studied sea anemone genus. J Proteome. 2017;166:83–92.
14. Orts BDJ, Peigneur S, Silva-Gonçalves LC, et al. AbeTx1 is a Novel Sea anemone toxin with a dual mechanism of action on shaker-type K^+ channels activation. Mar Drugs. 2018;16:360.
15. Isbister GK. Marine envenomations from corals, sea urchins, fish, or stingrays. UpToDate.
16. Sitprija V, Sitprija S. Marine toxins and nephrotoxicity: mechanism of injury. Toxicon. 2019;161:44–9.
17. D'Ambra I, Lauritano C. A review of toxins from Cnidaria. Mar Drugs. 2020;18:507.
18. Li A, Yu H, Li R, et al. Jellyfish Nemopilema nomurai causes myotoxicity through the metalloprotease component of venom. Biomed Pharmacother. 2022;151:113192.
19. Funk JA, Janech MG, Dillon JC, et al. Characterization of renal toxicity in mice administered the marine biotoxin domoic Acid. J Am Soc Nephrol. 2014;25:1187–97.
20. Wu CH. Palytoxin: membrane mechanisms of action. Toxicon. 2009;54:1183–9.
21. Deeds JR, Schwartz MD. Human risk associated with palytoxin exposure. Toxicon. 2010;56:150–62.
22. Podobnik M, Anderluh G. Pore-forming toxins in Cnidaria. Semin Cell Dev Biol. 2017;72:133–41.
23. Mizuno M, Ito Y, Morgan BP. Exploiting the nephrotoxic effects of venom from the sea anemone, Phyllodiscus semoni, to create a hemolytic uremic syndrome model in the rat. Mar Drugs. 2012;10:1582–604.
24. Mizuno M. Envenomation by cnidarians and renal injuries. In: The Cnidaria, past, present and future. Cham: Springer International Publishing; 2016. p. 623–35.
25. Spielman FJ, Bowe EA, Watson CB, Klein EF. Acute renal failure as a result of Physalia physalis sting. South Med J. 1982;75:1425–6.
26. Guess HA, Saviteer PL, Morris CR. Hemolysis and acute renal failure following a Portuguese man-of-war sting. Pediatrics. 1982;70:979–81.
27. Deekajorndech T, Kingwatanakul P, Wananukul S. Acute renal failure in a child with jellyfish contact dermatitis. J Med Assoc Thail. 2004;87(Suppl 2):S292–4.
28. Shinzato T, Furusu A, Nishino T, et al. Cowfish (Umisuzume, Lactoria diaphana) poisoning with rhabdomyolysis. Intern Med. 2008;47:853–6.
29. Cegolon L, Heymann WC, Lange JH, Mastrangelo G. Jellyfish stings and their management: a review. Mar Drugs. 2013;11:523–50.
30. Liu X, Zhang M, Jia A, et al. Purification and characterization of angiotensin I converting enzyme inhibitory peptides from jellyfish Rhopilema esculentum. Food Res Int. 2013;50:339–43.
31. Li R, Yu H, Yue Y, et al. In depth analysis of the in vivo toxicity of venom from the jellyfish Stomolophus meleagris. Toxicon. 2014;92:60–5.
32. Mariottini GL. Hemolytic venoms from marine cnidarian jellyfish: an overview. J Venom Res. 2014;5:22–32.
33. Zhang H, Wang Q, Xiao L, Zhang L. Intervention effects of five cations and their correction on hemolytic activity of tentacle extract from the jellyfish Cyanea capillata. PeerJ. 2017;5:e3338.
34. Alvarez C, Ros U, Valle A, et al. Biophysical and biochemical strategies to understand membrane binding and pore formation by sticholysins, pore-forming proteins from a sea anemone. Biophys Rev. 2017;9:529–44.
35. Prentis PJ, Pavasovic A, Norton RS. Sea anemones: quiet achievers in the field of peptide toxins. Toxins (Basel). 2018;10:36.
36. Leychenko E, Isaeva M, Tkacheva E, et al. Multigene family of pore-forming toxins from sea anemone Heteractis crispa. Mar Drugs. 2018;16:183.
37. Tsutsui K, Sato T. Identification of the two new, functional actinoporins, CJTOX I and CJTOX II, from the deep-sea anemone Cribrinopsis japonica. Toxicon. 2018;148:40–9.
38. Marcus EN. Overview of shellfish, pufferfish, and other marine toxin poisoning. UpToDate; 2023.
39. Alvarez C, Soto C, Cabezas S, et al. Panorama of the intracellular molecular concert orchestrated by Actinoporins, pore-forming toxins from sea anemones. Toxins (Basel). 2021;13:567.
40. Mizuno M, Nishikawa K, Yuzawa Y, et al. Acute renal failure after a sea anemone sting. Am J Kidney Dis. 2000;36:E10.
41. Maldonado E, Maillaud C, Barguil Y, Labadie M. Rhabdomyolysis during envenomation by Physalia sp envenomation in New Caldonia. Med Sante Trop. 2017;27:105–8.
42. Kim AY, Cho KH, Kang SH, et al. Hemolytic uremic syndrome caused by sea anemone sting: a case report. BMC Nephrol. 2021;22:14.

43. Hayakawa M, Suzuki C, Zhu Y, Anzai H. A case of sea anemone dermatitis associated with acute renal failure caused by Phyllodiscus semoni. J Eur Acad Dermatol Venereol. 2022;36:e919–20.
44. Buscetta G, Rizzo C, La Barbera L, et al. Severe case of rhabdomyolysis following jellyfish envenomation in the Mediterranean Sea. RMD Open. 2023;9:e003569.
45. Loy JS, Khoo CC, Arumugam T, et al. Rhabdomyolysis due to unidentified jellyfish envenomation in west Malaysian waters. Toxicon X. 2024;21:100170.
46. Cochat P, Larbre F. Nephrotic syndrome after a medusa sting. Pediatrie. 1988;43:419–20.
47. Mizuno M, Nozaki M, Morine N, et al. A protein toxin from the sea anemone Phyllodiscus semoni targets the kidney and causes a severe renal injury with predominant glomerular endothelial damage. Am J Pathol. 2007;171:402–14.
48. Martins RD, Jorge RJB, de Alves RS, et al. Renal effects of Bunodosoma caissarum crude extract: prostaglandin and endothelin involvement. Toxicon. 2017;138:78–81.
49. Barnes JH. Cause and effects in Irukandji stinging. Med J Aust. 1964;1:897–904.
50. Pereira P, Barry J, Corkeron M, et al. Intracerebral hemorrhage and death after envenoming by the jellyfish Carukia barnesi. Clin Toxicol (Phila). 2010;48:390–2.
51. Tibballs J, Li R, Tibballs HA, et al. Australian carybdeid jellyfish causing «Irukandji syndrome». Toxicon. 2012;59:617–25.
52. Gershwin L, Richardson AJ, Winkel KD, et al. Biology and ecology of Irukandji jellyfish (Cnidaria: Cubozoa). Adv Mar Biol. 2013;66:1–85.
53. Yanagihara AA, Wilcox C, Smith J, Surrett GW. Cubozoan Envenomations: clinical features, pathophysiology and management. In: The Cnidaria, past, present and future. Cham: Springer International Publishing; 2016. p. 637–52.
54. Geng X-Y, Wang M-K, Chen J-H, et al. Marine biological injuries and their medical management: a narrative review. World J Biol Chem. 2023;14:1–12.
55. Morabito R, La Spada G, Crupi R, et al. Crude venom from nematocysts of the jellyfish Pelagia noctiluca as a tool to study cell physiology. Cent Nerv Syst Agents Med Chem. 2015;15:68–73.
56. Robinson SD, Li Q, Bandyopadhyay PK, et al. Hormone-like peptides in the venoms of marine cone snails. Gen Comp Endocrinol. 2017;244:11–8.
57. Gao B, Peng C, Yang J, et al. Cone snails: a big store of Conotoxins for novel drug discovery. Toxins (Basel). 2017;9:397.
58. Wang Z, Wang X, Wang J. Recent advances in antibacterial and Antiendotoxic peptides or proteins from marine resources. Mar Drugs. 2018;16:57.
59. Sintsova O, Gladkikh I, Monastyrnaya M, et al. Sea anemone Kunitz-type peptides demonstrate neuroprotective activity in the 6-Hydroxydopamine induced neurotoxicity model. Biomedicines. 2021;9:283.
60. Suput D. Interactions of cnidarian toxins with the immune system. Inflamm Allergy Drug Targets. 2011;10:429–37.
61. Mariottini GL, Pane L. Cytotoxic and cytolytic cnidarian venoms. A review on health implications and possible therapeutic applications. Toxins (Basel). 2013;6:108–51.
62. Moreels L, Peigneur S, Galan DT, et al. APETx4, a Novel Sea anemone toxin and a modulator of the cancer-relevant Potassium Channel KV10.1. Mar Drugs. 2017;15:287.
63. Zhou Y, Liu G, Cheng X, et al. Antimicrobial activity of a newly identified Kazal-type serine proteinase inhibitor, CcKPI1, from the jellyfish Cyanea capillata. Int J Biol Macromol. 2018;107:1945–55.
64. Yap WY, Hwang JS. Response of cellular innate immunity to Cnidarian pore-forming toxins. Molecules. 2018;23:2537.
65. Hemmati S, Rasekhi KH. Polypharmacological Cell-penetrating peptides from venomous marine animals based on immunomodulating, antimicrobial, and anticancer properties. Mar Drugs. 2022;20:763.

13 Hemorrhagic Accidents Caused by *Lonomia obliqua*

Alaour Candida Duarte,
Verônica Verleine Hörbe Antunes, Elvino Barros,
Gabriela Vieira Steckert, Gabriel Sartori Pacini,
and Renata Asnis Schuchmann

13.1 Introduction

Lonomism is the envenomation caused by accidental contact with *Lonomia* caterpillars, and this is a public health priority in South America since it is relatively common but remains underestimated. Patients typically develop severe pain at the site of envenomation, followed by dizziness, headache, nausea, vomiting, and abdominal pain.

The *Lepidoptera*, which include butterflies and moths, constitute one of the largest orders of the *Insecta* class. More than 165,000 species have been identified worldwide, most of which are classified as agricultural and native forest pests, as they are phytophagous insects in their larval stage [1]. Only the genus *Lonomia* is known to cause systemic poisoning resulting from the inoculation of venom through the skin, with local or systemic hemorrhagic manifestations of variable intensity. In severe cases, acute kidney injury (AKI), stroke, and shock due to volume loss, which can lead to death [2–10]. *Lonomia* refers to a genus of venomous caterpillars belonging to the family *Saturniidae*, which are found primarily in South America. These caterpillars are medically significant due to the potent toxins present in their spines, which can cause severe hemorrhagic syndromes.

13.2 Epidemiology

The first description of the clinical and hemorrhagic manifestations caused by caterpillar poisoning in the Brazilian literature was reported by Alvarenga [2], in the case report of a 36-year-old adult, without a history of morbidity that touched a group of caterpillars with his right hand. Approximately 10 min later, he started having severe headache, flushing, and mild edema.

More recently, new cases of hemorrhagic accidents caused by *Lonomia obliqua* have started to draw attention in southern Brazil after the study by Duarte et al. [5] who presented two cases of AKI after contact with *Lonomia*, a previously unknown complication. The emergence of other cases in the southern region of Brazil, particularly in the state of Rio Grande do Sul, is analyzed by Kelen et al. [6]

In the municipality of Passo Fundo, South Brazil, 155 patients diagnosed with *Lonomia* accidents were treated from December 1989 to

A. C. Duarte
School of Medicine, University of Passo Fundo, Passo Fundo, Rio Grande do Sul, Brazil

V. V. H. Antunes · E. Barros (✉)
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil
e-mail: vantunes@hcpa.edu.br

G. V. Steckert · G. S. Pacini· R. A. Schuchmann
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brasil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_13

February 1994. These cases started in the northern region of the state of Rio Grande do Sul. There are a lot of reports from another Brazilian States: Santa Catarina, Paraná, São Paulo, and Minas Gerais. Between 1997 and 2017, the Toxicological Information Center of Rio Grande do Sul (CIT-RS) treated 13,583 cases of poisoning due to accidents with *Lonomia obliqua*, with a significant reduction in cases in recent years; for instance, only 34 cases were reported in 2017 [7]. Since the 1990s, the Ministry of Health has routinely introduced a routine treatment for these events, which includes the availability of antilonomic serum since 1996.

Recent study presents an updated and integrative analysis of reliable global data from 1960 to 2020 on the epidemiology of this envenomation in the whole continent. A total of 13,186 notifications were recorded for South America: 13,056 (99.01%) in Brazil, 49 (0.37%) in Argentina, 43 (0.33%) in Colombia, 29 (0.22%) in Venezuela, six (0.05%) in Peru, and three (0.02%) in French Guiana. The number of new locations reporting accidents has increased since the first formal notifications at the middle of the last century. Most of these locations are situated in Brazil, the pioneer in deeply researching the *Lonomia* genus and its impacts in public health [8].

13.3 *Lonomia* Venom Mechanism of Action

Arocha-Piñango et al. [9] suggest the presence of a double mechanism of action for *Lonomia achelous* venom, the main causative agent of hemorrhagic cases in Venezuela. Intense fibrinolytic action and a picture similar to disseminated intravascular coagulation would account for extremely low plasma levels of fibrinogen, plasminogen, and other coagulation factors. They observed that the levels of fibrin degradation products were not proportional to the intensity of the observed hemorrhage, postulating that during the fibrinogen/fibrin molecule degradation, injury could occur in sites that are important for the thrombin-fibrinogen reaction inhibition. The detection of thrombin antithrombin complexes indicated that thrombin formation would occur, perhaps by a component similar to factor X activator, thus suggesting a procoagulant activity of the venom.

The persistence of extremely low levels of factor XIII suggested to Arocha-Piñango et al. [9] that it is a good substrate for some enzymes present in *Lonomia* caterpillar hairs. This finding could explain the intense fibrinolytic activity in the patients' blood, since the crosslink between a_2–antiplasmin and fibrin is mediated by activated factor XIII in the clot lysis control.

13.4 Clinical Picture

Alvarenga [2] described the clinical and hemorrhagic manifestations caused by caterpillar poisoning. After 10 min of contact with a caterpillar colony, the 32-year-old patient started to show severe headache, flushing, edema, and mild ascending lymphangitis up to the armpit region.

On the following day, upon awakening, he felt his mouth full of liquid, which consisted of saliva with dark blood. He forced sputum production, which came out clean, and exercised pressure on his tongue and gums, producing no blood. But saliva from the salivary glands continued to appear bloody.

The first morning urine was bloody and the other urinations too. Prior to the accident, he had a minor hand injury that did not bleed immediately but bled hours later. At dawn on the 5th day, he started to have severe low back pain without irradiation. The hematuria persisted throughout the day. The author considered scurvy, purpura, hemophilia, kidney stones, and finally caterpillar envenomation. At that time, the author mentioned the similarity of caterpillar venom to that of snakes of the *Bothrops* and *Lachesis* genus.

Between 1960 and 1967, five cases of acute hemorrhagic syndrome following contact with caterpillars were studied by Arocha-Piñango [11] in Venezuela. In addition to the local symptoms of burning sensation and severe pain, the patients had headache, pain, and generalized malaise: between 8 and 72 h after the onset of the first symptoms, the hemorrhagic condition was characterized by epistaxis, otorrhagia, enterorrhagia, metrorrhagia, and generalized hematomas.

In addition to local manifestations and general symptoms, patients had malaise, headache,

nausea, and vomiting, bleeding 1–12 h after contact, such as hematomas, epistaxis, bleeding from recent wounds, gum bleeding, hematuria, and pulmonary hemorrhage. Hemorrhagic stroke may also occur, and the first death caused by *Lonomia* poisoning in the state of Rio Grande do Sul was due to intracranial hemorrhage, as reported by Duarte et al. [12] AKI occurred in six patients and there were four deaths.

In brief, the clinical manifestations are:

1. Symptoms at the contact site:
   Burning pain, which may be accompanied by edema and erythema of varying intensity and duration, depending on the characteristics of each patient.
2. Nonspecific general manifestations:
   Holocranial headache, general malaise, nausea and vomiting, anxiety, myalgia, and, less frequently, abdominal pain and hypotension.
3. Hemorrhagic manifestations:
   After a period ranging from 1 to 48 h, blood dyscrasia occurs, accompanied by hemorrhagic manifestations.

Bleeding episodes usually appear within 72 h after contact, including hematomas that can lead to extensive hemorrhagic suffusions, spontaneous bruising, bleeding from recent wounds, healed lesions, bleeding from mucosal cavities (gingival, epistaxis, hematemesis, enterorrhagia), intraarticular, abdominal (intra- and extraperitoneal), pulmonary, thyroid bleeding, and intraparenchymal cerebral hemorrhage.

Bleeding episodes can occur in the most diverse anatomical locations, which, depending on the volume, can result in severe clinical manifestations.

13.5 Laboratory Tests

The morphological study of peripheral blood showed anemia with reticulocytosis, normal platelet and white blood cell counts, except for one patient who had leukocytosis with neutrophilia. Clotting time (CT) was infinite in one case, prolonged in two, and normal in the others (the latter had received fibrinogen hours before the collection). Fibrinogen levels were decreased in all cases (<100 mg/L). In cases where clot formation was observed, the clot completely dissolved within 5–120 min.

13.6 Diagnosis

The identification of the caterpillar is crucial and can be done through pictures or by a specialized person. The time of contact and the number of caterpillars may be related to severity. A clotting time (CT) test should be promptly requested:

- If the blood clots within 8–12 min and does not redissolve within 1 h (it is noteworthy that, redissolution of the clot means the same risk as anticoagulation).
- If the identification was positive for *Lonomia*, repeat CT in 12–24 h.
- If CT is altered, request blood count, fibrinogen, creatinine, Quantitative Urine Test, and platelets.
- If hematuria or creatinine is elevated, monitor urinary volume and classify AKI using RIFLE or AKIN or KDIGO criteria.

Renal replacement therapy (RRT) indication should follow the nephrologist's criteria.

- If there are neurological signs, such as severe headache, sensory decrease, and motor or sensitivity alteration, a computed tomography assessment of the skull should be performed.

Accidents should be must classified according to the severity:

Grade I: Local manifestations only.
Grade II: CT alteration, without hemorrhagic manifestations.
Grade III: CT alteration with hemorrhagic manifestations.

13.7 Treatment of Hemorrhagic Syndrome

Most reactions to *Lepidoptera* are mild and self-limited and require only removal of visible embedded spines and symptomatic relief. Pain from caterpillar envenomation may be treated with ice or topical and oral analgesia.

Treatment of lonomism typically requires inpatient supportive care. Rapid administration of an antilonomic serum developed in Brazil for envenomation by *L. obliqua* appears effective for reversing coagulation time and may reduce fatalities, although data are limited.

The antilonomic serum is given intravenously in a single treatment session. A Brazilian trial in which 44 patients who developed laboratory evidence of hemorrhagic syndrome after contact with *L. obliqua* were randomly assigned to either 10.5 mg or 17.5 mg of antilonomic serum found similar laboratory and clinical outcomes for patients in both groups.

Grade I: Removal of caterpillar hairs, if present, with tweezers and local ice application. If the local reaction is too intense with lymphangitis, antihistamines, and/or corticosteroids should be prescribed.

Grade II: 5 ampoules of antilonomic serum.

Grade III: 10 ampoules of antilonomic serum.

Normally, 1 h after the serum administration, the blood starts again to coagulate, allowing craniotomy-type surgeries to be performed, as was the case with a child in our department who had an extradural hematoma.

The following are the complications:

Acute kidney injury—nephrologist

Intracranial hemorrhage—neurologist

If surgical procedure is required, wait 1 h after administration of the antilonomic serum.

13.8 Prognosis

The prognosis will depend on the severity of the accidents. Patients with Grade I and II showed 100% recovery, while patients in Grade III had acute kidney injury (AKI) as the main complication, which occurs in 15–18% of cases. Patients over 50 years of age are the ones who develop AKI. Another risk factor is the time elapsed between the accident and medical care, and most patients with AKI arrived 48 h after the accident. Risk factors for AKI development are as follows:

- Age over 50 years
- Delay in seeking medical attention (more than 48 h)
- Active bleeding

Blood, plasma, or cryoprecipitate replacement therapy increases the risk of new bleeding episodes and AKI development. Of the patients who develop AKI, approximately 50% required renal replacement therapy (RRT).

The lethality of *Lonomia* envenomation was three to four times higher than that recorded for that of snakebite accidents in Brazil, thus reflecting the severity of this poisoning. Health professionals' lack of knowledge may have interfered with case evolution, as delayed care may have contributed to the lethal outcome. The most frequent cause of death is intracerebral hemorrhage.

References

1. Pesce H, Delgado A. Lepdopterism and erucismo. Epidemiology and clinical aspects in Peru. Mem Inst Butantan. 1966;33(3):829–34.
2. Alvarenga Z. A taturana. Rev Fac Med USP, Ann VII Cong Bras Med Cir. 1912;II:132–5.
3. Arocha-Piñango CL, Layrisse M. Fibrinolysis produced by contact with a Caterpillar. Lancet. 1969;1(7599):810–2.
4. Fraiha H, Ballarini AJ, Leão RNQ, et al. Síndrome hemorrágica por contato com larvas de mariposa (Lepidoptera, Saturniidae). In: Inst. Evandro Chagas, 50 anos de contribuição às ciências biológicas e à medicina tropical, vol. 2. Belém: Fundação Serviços de Saúde Pública; 1986. p. 811–8.
5. Duarte AC, Caovilla J, Lorini I, et al. Insuficiência renal aguda por acidentes com lagartas. J Bras Nefrol. 1990;12(4):184–7.
6. Kelen EMA, Picarelli ZP, Duarte AC. Hemorrhagic syndrome induced by contac with caterpillars of the genus *Lonomia* (*Saturniidae*, *Hemileucinae*). J Toxicol Toxin Ver. 1995;14(3):283–308.

7. Favalesso MM, Cuervo PF, Casafús MG, Guimarães ATB, Peichoto ME. Lonomia envenomation in Brazil: an epidemiological overview for the period 2007–2018. Trans R Soc Trop Med Hyg. 2021;115(1):9–19.
8. Favalesso MM, Valentim M, Guimarães ATB, Peichoto ME. Epidemiological characterization of lonomism in South America. Acta Trop. 2023;238:106777. https://doi.org/10.1016/j.actatropica.2022.106777. Epub 2022 Dec 9
9. Arocha-Piñango CL, de Bosch NB, Noeul AL, et al. Fibrinolytic and procoagulant agents from a Saturnidae moth caterpillar. In: Pirkle H, Markland FS, editors. Hemostasis and Animal Venoms. New York: Marcel Dekker; 1988. p. 223–40.
10. Arocha-Piñango CL, de Bosch NB, Torres A, et al. Six new cases of caterpillar-induced bleeding syndrome. Tromb Haemost. 1992;67(4):402–7.
11. Arocha-Piñango CL. Fibrinolisis producida por contacto com orugas: comunicacíon preliminar. Ata Cient Venezolana. 1967;18:136–9.
12. Duarte AC, Crusius OS, Pires CAL, et al. Intracerebral haemorrhage after contact with *Lonomia caterpillars*. Lancet. 1996;348:1033.

Part IV

Virus-Associated Kidney Diseases

14 Kidney Involvement in Arboviral Diseases: Chikungunya, Dengue, and Zika

Roberto da Justa Pires Neto,
Denise Maria do Nascimento Costa,
and Geraldo Bezerra da Silva Junior

14.1 Introduction

Arboviruses are viruses belonging to different families with one characteristic in common: they are transmitted to humans and other animals through the bite of hematophagous arthropods. Arboviruses are diseases caused by arboviruses, the most common being chikungunya, dengue, and Zika [1].

The clinical spectrum of this group of diseases varies, and there may be asymptomatic forms; mild forms, usually of a febrile nature, accompanied by exanthematous rashes (acute exanthematous febrile disease); and severe forms, characterized by hemorrhagic manifestations (hemorrhagic fever), neurological, cardiovascular, renal, among others. Complications involving specific systems and organs, including the kidneys, are increasingly observed and appear to have important repercussions on morbidity/mortality related to arboviruses. Arboviruses are found mainly in regions with tropical and subtropical climates and are considered hyperendemic in regions of Asia and Latin America, especially in Brazil [1, 2].

The arboviruses of greatest importance to public health are dengue, chikungunya and Zika, all capable of being transmitted by the same vectors, mainly *Aedes aegypti* and *Aedes albopictus* [3].

For several years, Brazil has reported epidemics of dengue fever and, more recently, chikungunya, and Zika, with a large increase in cases observed in recent years, mainly in urban centers [4]. This process of urbanization of arboviruses is mainly due to climatic conditions/increased temperatures, which favor the proliferation of these vectors, and the deficient infrastructure of basic sanitation services offered in Brazil [4, 5].

This chapter aims to describe the most common arboviruses in Brazil, their clinical and epidemiological characteristics, emphasizing aspects related to renal involvement in these diseases. The chapter initially addresses biological, epidemiological, and clinical aspects of each arbovirus. The main scientific evidence on renal involvement in these arboviruses is then presented.

R. da Justa Pires Neto
Department of Community Health, School of Medicine, Federal University of Ceara, Fortaleza, Ceara, Brazil
e-mail: robertojusta@ufc.br

D. M. do Nascimento Costa
Faculty of Medicine of Recife, Federal University of Pernambuco, Recife, Pernambuco, Brazil
e-mail: denise.costa@ufpe.br

G. Bezerra da Silva Junior (✉)
Post-Graduation Programs in Public Health and Medical Sciences, School of Medicine, University of Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_14

14.2 Chikungunya

Chikungunya is an arbovirus caused by a virus of the *Togaviridae* family and the *Alphavirus* genus. The main form of transmission occurs through the bite of the female *Aedes aegypti* and *Aedes albopictus mosquito* infected by the virus [2]. Although rare, vertical transmission may also occur, mainly during the intrapartum period in viremic pregnant women, and transmission via transfusion [2, 6]. It has an average incubation period of 2–4 days, which can vary between 1 and 14 days [6]. The Ministry of Health defines a suspected case of chikungunya as any individual who presents with a sudden-onset fever greater than 38.5 °C and severe arthralgia or arthritis of acute onset, not explained by other conditions, coming from areas with transmission up to 2 weeks from the onset of symptoms, or who has an epidemiological link with a confirmed imported case [7].

14.3 Epidemiology

Chikungunya is listed as one of the World Health Organization's (WHO) priority diseases and has been detected in more than 100 countries in Asia, Africa, Europe, and the Americas. Epidemics with more than 200,000 cases have already been recorded in countries in Africa and the Caribbean [6] (Fig. 14.1).

In Brazil, chikungunya was introduced in 2014, and the first major epidemic occurred in 2016, when more than 277,000 probable cases and 318 confirmed deaths from the disease were recorded. In 2023, 154,800 new probable cases of chikungunya were reported, with 106 confirmed deaths from the disease. In 2024, by the end of April, more than 100,000 suspected cases of chikungunya had been recorded in Brazil [7].

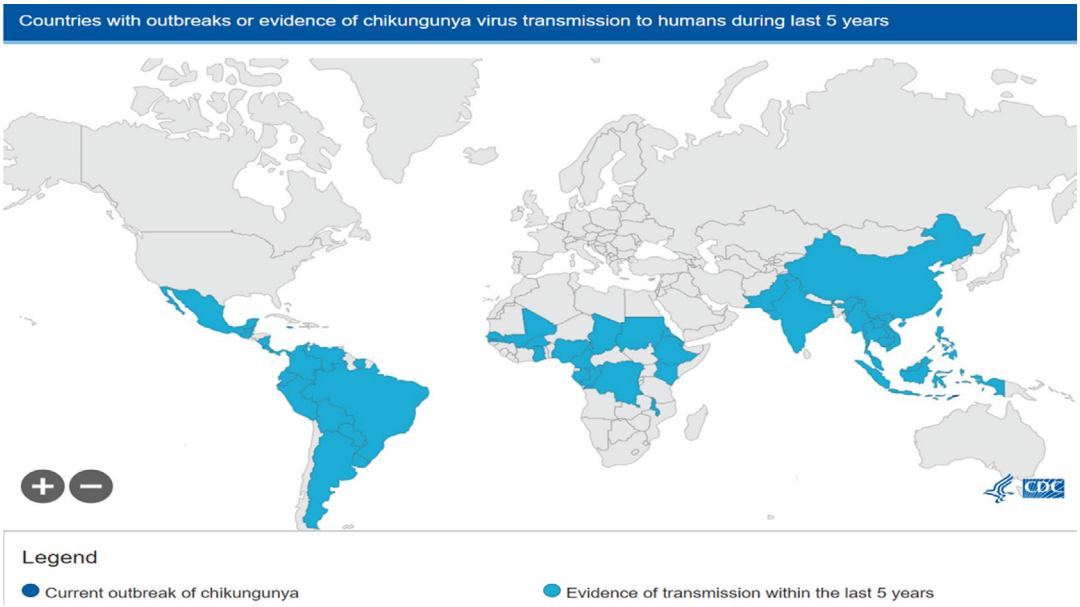


Fig. 14.1 Worldwide distribution of Chikungunya cases. (Source: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Vector-Borne Diseases (DVBD). Last updated: March 2024. https://www.cdc.gov/chikungunya/geo/index.html)

14.4 Clinical and Laboratory Manifestations

Although rare, chikungunya can be asymptomatic in 3–5% of cases. However, most affected patients typically present with fever and joint pain. Fever usually lasts 3–5 days. Intense joint pain is the most characteristic symptom of chikungunya, whose term in the African Makonde language means "those who bend," due to the hunched appearance often found in affected patients. Arthralgia usually appears 2–4 days after the onset of fever and frequently affects several joints symmetrically. Macular or maculopapular rash may appear in half of affected individuals, between the 2nd and 5th day after the onset of fever. Other clinical presentations of chikungunya include atypical manifestations, such as neurological, cardiovascular, and renal involvement [8, 9].

In general, the acute signs and symptoms of chikungunya tend to resolve within 1–2 weeks after the onset of clinical manifestations. However, the disease can progress to a subacute phase, with symptoms lasting between 15 days and 3 months, and a chronic phase, when symptoms persist for more than 3 months [10, 11]. In the chronic phase, the most prevalent symptom is arthralgia, which can occur in more than half of patients after 15 months of infection [12, 13].

Laboratory findings of chikungunya are nonspecific and include lymphopenia and thrombocytopenia. Diagnostic confirmation is performed by viral isolation, real-time PCR (RT-PCR), and detection of anti-chikungunya IgM antibodies (collected during the acute or convalescent phase). A fourfold increase in the titer of specific IgG antibodies in the acute and chronic phases, preferably collected 15–45 days after the onset of symptoms, or 10–14 days after the acute phase, also confirms the diagnosis [2, 14, 15].

14.5 Pathophysiology of Renal Involvement

The pathophysiology of renal involvement in chikungunya is illustrated in Fig. 14.2. The mechanisms of renal injury associated with chikungunya are not yet fully understood. In general, it possibly results from immunological alterations common to other viral infections, such as the expression of aberrant proteins and dysregulation of cellular homeostasis, especially in patients who are genetically susceptible [16, 17]. Chikungunya can also cause an imbalance in the immune response, with the production of IgM antibodies and the formation of autoantibodies, including cryoglobulins, which have properties that cause renal damage [17]. In addition, the chi-

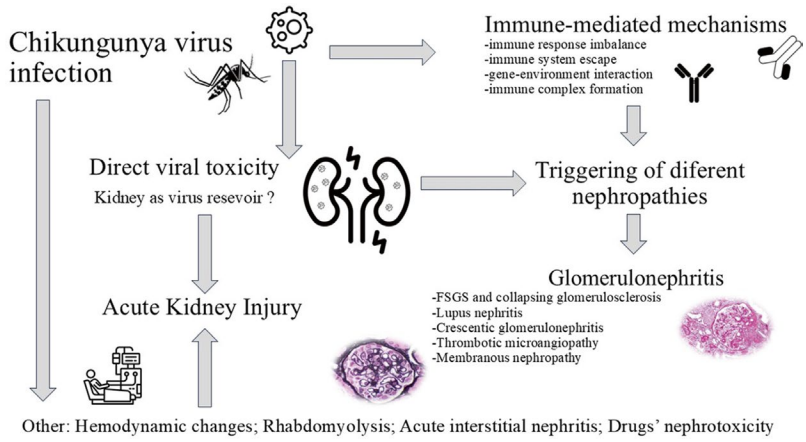


Fig. 14.2 Pathophysiology of renal involvement by the Chikungunya virus

kungunya virus has been detected in the glomeruli of infected patients, in the interstitial space and in the tubular epithelium [18]; however, there was no evidence that it exerts a direct cytopathic effect. There is also no evidence that the degree of viremia alone has a direct relationship with the chance of developing renal injury [18–23]. Other possible causes of kidney damage in chikungunya are those related to complications of the infection or its treatment, including hemodynamic changes and rhabdomyolysis [24].

Acute kidney injury (AKI) associated with chikungunya occurs more frequently in patients with atypical presentations and severe cases of the infection [25, 26]. In hospitalized patients with severe forms of chikungunya, the incidence of AKI reaches 18% [9]. Among those hospitalized in intensive care settings, this incidence can reach 79% and approximately 27% of these patients may require renal replacement therapy (RRT) [27, 28].

Prerenal AKI is the most common form of chikungunya, described in approximately 20% of patients, and may also occur as a complication of previous chronic kidney disease (CKD) [15, 29]. Case reports and series also demonstrate other different forms of renal involvement resulting from chikungunya, including those related to multiple organ and system dysfunctions [30], thrombotic thrombocytopenic purpura [31, 32], and rhabdomyolysis [33, 34] and glomerulopathies [17, 35]. Findings such as hematuria and proteinuria can be detected in approximately 2–20% of patients [15, 36]. Therefore, in addition to urea and creatinine, urinalysis should be part of the investigation of every patient with severe chikungunya or suspected AKI, enabling early diagnosis of kidney lesions triggered by the infection.

Little is known about the prognosis of patients with chikungunya-associated AKI. In a case series of 16 patients with chikungunya-associated AKI of glomerular etiology, in most cases, there was progression to CKD in 56% of cases after 12 months of follow-up, and two patients remained dependent on dialysis at the end of this study [17].

The impact that AKI associated with chikungunya has on the patient's outcome is also not well established. In a large series of patients with atypical chikungunya, renal manifestation did not alter the prognosis of the infection [15]. On the other hand, some studies show that patients who present AKI at the time of diagnosis or during the infection have a greater chance of hospitalization compared to those without AKI [37]. Although it is a matter of controversy, AKI also appears to be associated with an increased chance of mortality not only in elderly patients but also in the general population affected by chikungunya [38–42].

There is also evidence of the negative impact of pre-existing CKD on the outcome of patients with chikungunya, being associated with a greater need for hospitalization [43] and higher mortality [44, 45]. In kidney transplant recipients, however, although some patients experience a transient increase in serum creatinine in the acute phase of the disease, the course of the infection typically does not appear to be different compared with non-kidney transplant patients [46].

14.6 Renal Histopathological Findings

Renal histopathological evaluation in patients affected by chikungunya is still little studied and, in most studies, performed in the acute phase of the disease. Analysis of postmortem renal tissue in two series of patients affected by chikungunya detected a predominance of acute interstitial nephritis, present in 21 of 24 cases evaluated. Findings such as mononuclear infiltrate, acute tubular necrosis, and interstitial fibrosis, in addition to glomerular edema/congestion, nephrosclerosis, and one case of membranoproliferative glomerulonephritis have also been described [18, 47]. Other case reports performed with in vivo renal tissue described new findings such as nonnecrotizing giant cell granuloma, focal segmental glomerulosclerosis (FSGS), tubular myoglobin casts in a patient

with rhabdomyolysis, and renal thrombotic microangiopathy due to atypical hemolytic-uremic syndrome triggered by chikungunya [48, 49]. Furthermore, the presence of viral antigen in the renal tissue of patients with chikungunya-associated AKI was demonstrated. Through immunohistochemistry and immunofluorescence, viral material was detected in vessels, glomeruli, interstitial tissue, tubular epithelium, and inflammatory infiltrate of the patients evaluated, but no direct cell damage caused by the virus was evidenced [18, 23].

Because this is an infection with the potential for chronicity, with evidence of persistence of viral material in lymphoid and joint tissues [50, 51], renal samples from 15 patients with evidence of renal injury in the subacute and chronic phases of chikungunya were also evaluated [17]. The histopathological findings were diverse, with a predominance of glomerulopathies (FSGS, lupus nephritis, collapsing glomerulopathy, membranous nephropathy, crescentic glomerulonephritis, pauci-immune), in addition to new cases of thrombotic microangiopathy. Due to the detection of some genotypes at risk for renal injury, without evidence of viral material in renal tissue, this study strengthens the hypothesis that the chikungunya virus acts as a trigger for the development of AKI in genetically susceptible individuals. Renal histopathological findings of patients with chikungunya are illustrated in Fig. 14.3.

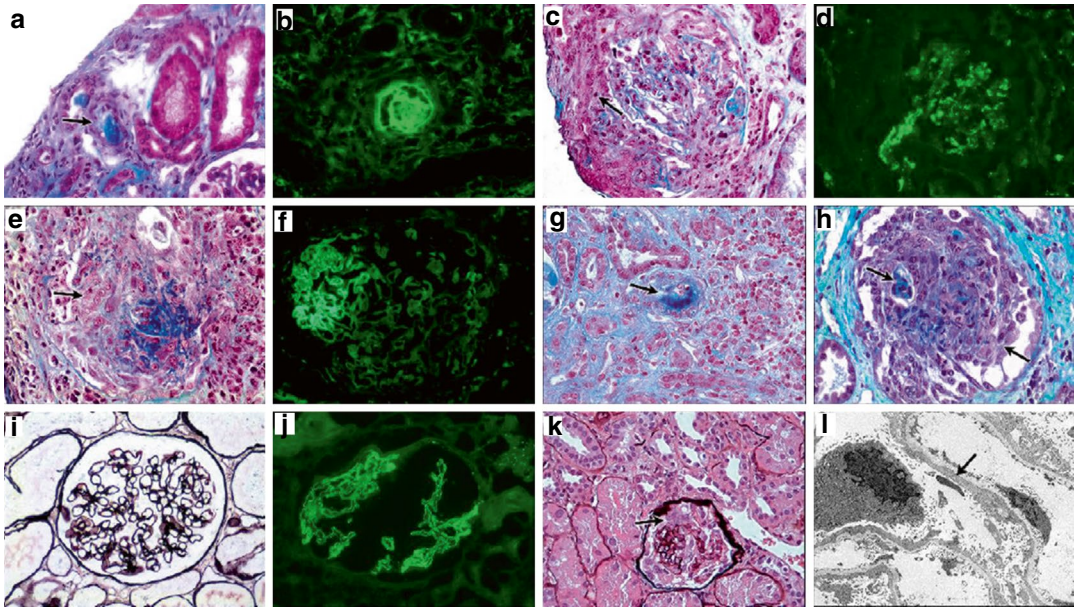


Fig. 14.3 Renal histopathological findings of 11 patients with Chikungunya. (1. Thrombotic microangiopathy (Patient 1): (**a**) Arteriolar occlusive thrombus (arrow, Masson's trichrome stain); (**b**) Arteriolar fibrinogen deposition on immunofluorescence. 2. Class IV lupus nephritis (Patient 2): (**c**) Proliferative glomerulonephritis with circumferential crescents (arrow, Masson's trichrome stain); (**d**) Strongly positive C1q on immunofluorescence. 3. Crescentic necrotizing glomerulonephritis (Patient 4): (**e**) Destructive fibrinoid necrosis and cellular crescent (arrow, Masson's trichrome stain); (**f**) Strong focal segmental staining for fibrinogen seen in the glomerulus. 4. Thrombotic microangiopathy and necrotizing crescentic glomerulonephritis (Patient 3): (**g**) Intraluminal fibrin thrombus (arrow, Masson's trichrome stain); (**h**) Crescent and fibrinoid deposit (arrow, Masson's trichrome stain). 5. Stage I membranous nephropathy (Patient 5): (**i**) Normal appearance on silver stain; (**j**) Diffuse and strongly stained, finely granular pattern, uniformly distributed (pseudolinear) in the glomerular capillary wall with IgG (immunofluorescence). 6. Collapsing glomerulopathy (Patient 10): (**k**) Pseudocrescents: Podocyte cell hypertrophy and hyperplasia (silver stain); (**l**) Ultrastructural analysis showed diffuse effacement of podocytes (arrow). Original magnification: **a**, **b**, **c**, **d**, **e**, **f**, **g**, **h**, **i**, **j**, **k** 400×; **l**, 4000×. (Adapted from Costa et al. [18])

14.7 Treatment

There is no specific antiviral treatment for chikungunya. Symptomatic treatment includes rest, hydration, and use of analgesics and antipyretics. The use of nonsteroidal anti-inflammatory drugs is not recommended. For cases of AKI associated with chikungunya, there is no specific treatment. Supportive measures for AKI are recommended, in addition to treatment of specific lesions, such as glomerulopathies and thrombotic microangiopathy, as per usual recommendations. The best form of treatment, however, is prevention of the disease with control measures against the mosquito vector and vaccination. The VLA1553 vaccine, not yet approved in Brazil, was approved by the FDA in 2023, with the capacity to generate neutralizing antibodies in 98.5% of volunteers 28 days after the application of a single dose [52, 53].

14.8 Dengue

Dengue is a disease caused by a virus of the *Flaviviridae* family, with four serotypes (DENV 1–4), whose main transmitting agent is the mosquito *Aedes aegypti*. Dengue can manifest itself from asymptomatic infection to severe disease with multiple organ failure. Currently, dengue is a major public health problem due to its wide distribution throughout the world (endemic disease in more than 100 countries) and the large number of people exposed to the risk of being infected [3].

14.9 Epidemiology

Dengue is the most prevalent arbovirus in the world, being present in five of the six WHO regions, with epidemic cycles in the Americas every 3–5 years. In 2023, there was a historic peak in the incidence of dengue in the world, with more than five million cases registered. Brazil was the country with the highest incidence of the disease, with more than half of the world's cases, with the highest incidence rates in the South (1269.8 cases/100,000 inhabitants) and Southeast (1028.6 cases/100,000 inhabitants) regions [7]. In the same year, 21,624 cases of dengue with warning signs and severe dengue were confirmed, and 946 deaths, with a fatality rate of 4.4% [7]. In 2024, by the end of April, more than four million cases of dengue had been registered in Brazil, a historic record, representing the largest epidemic of the disease in our country [7].

14.10 Clinical and Laboratory Manifestations

Dengue should be suspected in any individual with recent onset of fever and at least two of the following manifestations: headache, prostration, muscle and/or joint pain, and retro-orbital pain. The clinical manifestations of dengue vary from asymptomatic disease, through undifferentiated febrile illness, to severe forms or unusual manifestations including multiple organ failure. Since 2009, the clinical manifestations of dengue have been classified as dengue with or without warning signs and severe dengue [3].

In dengue, fever typically lasts 2–7 days. The rash occurs in approximately 50% of cases and is characterized mainly by the presence of macules and papules, which may or may not be pruritic. The rash usually affects the face, trunk, and limbs, not sparing the palmoplantar region, and appears most commonly after the fever has disappeared. In severe forms of the disease, neurological impairment may occur during the febrile period or later, in the convalescent phase. Clinical presentations are varied and include the presence of lymphocytic meningitis, encephalitis, Reye's syndrome, polyradiculoneuritis and Guillain-Barré syndrome [3].

Laboratory confirmation of dengue fever can be performed using several methods and depends on the stage of the disease. In the acute phase, up to the fifth day of the disease, the diagnosis can be made by detecting viral antigens such as NS1, viral isolation in cell culture, RT-PCR and immunohistochemistry. The diagnosis of dengue fever after the fifth day of the disease should be made

through serology (*Enzyme-Linked Immunosorbent Assay*—ELISA method) with detection of IgM antibodies. Previous infection can also be investigated through ELISA with detection of specific IgG antibodies [3].

14.11 Renal Involvement

Renal manifestations in dengue are relatively common and, in most cases, mild. Hyponatremia is the most common electrolyte abnormality in dengue [54]. Hyponatremia may be caused by several mechanisms that may act simultaneously: excess endogenous water due to increased metabolism; inappropriate and transient secretion of antidiuretic hormone leading to increased tubular reabsorption of water; and influx of sodium into cells due to dysfunction of the sodium-potassium pump. Other factors such as low salt intake, vomiting, and diarrhea may contribute to the hyponatremia observed in many patients with dengue [55].

Another electrolyte alteration observed in dengue is hypokalemia, which has been reported in 14–28% of dengue patients. Evidence suggests that a combination of mechanisms may be responsible for the hypokalemia observed in dengue patients. Hira et al. [56] reported 10 (8%) patients with serum potassium <3.0 mEq/L. None of these patients had an obvious cause of hypokalemia such as low dietary intake, drugs, intravenous fluid infusion, or gastrointestinal loss. Hypokalemia in these cases may have been due to a transient renal tubular abnormality leading to increased urinary potassium loss, or due to redistribution of potassium into cells. Increased renal potassium excretion due to activation of the renin-angiotensin-aldosterone system secondary to volume depletion has also been suggested as a causative mechanism of hypokalemia in dengue [55, 57, 58].

Proteinuria is the most common urinary alteration observed in dengue. In a study conducted with patients hospitalized with dengue in Australia, hematuria and proteinuria were observed in 31% and 74%, respectively. In another study, Jayarajah et al. [59] found microalbuminuria in 65.9% of patients and nonnephrotic proteinuria in 15.3% of patients with dengue. In this series, the presence of proteinuria was associated with advanced age, elevated liver enzymes, thrombocytopenia, and neutropenia. In most cases, proteinuria in dengue is self-limited and of short duration. However, there are reports of patients with dengue with nephrotic-level proteinuria. The high frequency of urinary alterations observed in some studies suggests that renal involvement is common in patients with dengue, but with poorly understood mechanisms. The proteinuria observed appears to be due to autoimmune glomerulonephritis triggered by the virus. In addition, several studies have reported glomerular damage mediated by immune complexes [55, 59].

AKI is a frequently reported complication of dengue fever and can significantly affect the morbidity and mortality of these patients. It usually occurs in severe cases of dengue fever, affecting approximately 3–4% of cases [24, 60]. Mallhi et al. [61] identified AKI as significantly associated with severe dengue, diabetes mellitus, nephrotoxic drugs, and rhabdomyolysis. Although mild creatinine elevation is common in dengue cases, clinically significant AKI is less common. The incidence of AKI in patients with severe dengue is variable and subject to different criteria used in different studies. Lee et al. [62] reported AKI in 3.9% of patients with severe dengue in Taiwan. Wiwanitkit [63] reported AKI in 0.3% of dengue cases, and the occurrence of AKI was 33.3% among fatal dengue cases. Advanced age, male sex, previous history of stroke or CKD, gastrointestinal hemorrhage, concomitant bacteremia, low hemoglobin and serum albumin levels, prolonged prothrombin time, and elevated liver enzymes were associated with a higher risk of AKI in dengue patients.

The mechanisms involved in the development of AKI in patients with dengue are varied. Dengue causes increased capillary leakage and consequent reduction in intravascular volume. This may result in reduced renal perfusion, leading to acute tubular necrosis (ATN). There are reports in the literature of cases of ATN in patients with dengue, even without progression to severe

dengue. Another reported mechanism has been coagulopathy combined with hypotension as the primary cause of AKI in dengue. Both the intrinsic and extrinsic coagulation cascades may be altered in dengue. Furthermore, several studies have identified a strong association of acute hemolysis, hypotension, and renal injury in patients with dengue and AKI. Myoglobinuria has been reported in patients with AKI and dengue. Immune complex-mediated glomerular damage has also been suggested as a mechanism of AKI in dengue, since glomerular deposits of IgG, IgM, and C3 were found in these patients. Finally, there is evidence that the dengue virus itself can cause direct renal damage. The presence of viral particles in renal tissue has been reported in postmortem studies, and immunohistochemical techniques have found viral antigens in the renal tubules of patients with confirmed dengue infection. The pathophysiology of renal involvement in dengue is illustrated in Fig. 14.4.

Most dengue patients who develop AKI have a relatively benign course, with some patients requiring hemodialysis for a brief period. Most of these patients recover renal function without sequelae within 2 weeks of progression. A few studies have reported the presence of AKI in fatal cases of dengue. Kuo et al. [64] for example, reported a significantly higher mortality rate among patients with dengue and AKI (28.6%) than among dengue patients without AKI (1.2%). The high morbidity and mortality observed in cases of dengue and AKI point to the need for early identification and treatment of these patients. The long-term effects of AKI, even if reversed, on the survival and renal function of patients with dengue are still unknown [55, 61].

The diagnosis and treatment of dengue hemorrhagic fever (DHF) in patients with CKD can be difficult. The overlapping signs and symptoms (reduced urine output, hemoconcentration, pleural effusion, and ascites) common to both conditions pose a challenge. Complications, including increased mortality, may occur in patients with CKD [65, 66]. A delay in diagnosis associated with reduced fluid tolerance has the potential to reduce the chances of successful fluid and electrolyte replacement in patients with CKD and DHF. Monitoring urine output in these patients is often impossible as a parameter for volume replacement. The risk of acute pulmonary edema is real. Hemodialysis is not always possible in patients with shock/hemorrhage. Mortality in these patients is considerably high [44].

Kidney transplant patients with dengue fever may develop a temporary loss of graft function, which usually recovers after the infection [67, 68]. These patients undergo immunosuppressive therapy, which reduces the chances of developing the immune response necessary for the occurrence of severe dengue fever. Thus, kidney transplant patients are less likely to develop severe forms of dengue fever. However, the occurrence of severe dengue fever is a potential risk for both

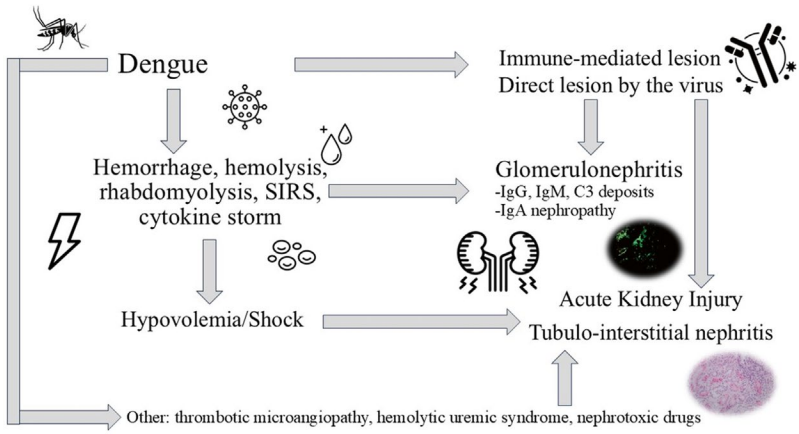


Fig. 14.4 Pathophysiology of renal involvement by the Dengue virus

the donor and the kidney recipient, especially in the early postoperative period. The occurrence of hypovolemia, common in cases of severe dengue fever, may contribute to damage to the newly grafted kidney. Hypoalbuminemia, also common in severe forms of dengue fever, may compromise the healing of surgical incisions and sutures of the transplanted kidney [69].

14.12 Treatment

Dengue is treated with symptomatic medication and clinical support measures, and there is no specific antiviral therapy [70]. There is a WHO guideline for the management of dengue [71]. Patients should be warned not to take anti-inflammatory drugs due to the risk of bleeding, especially in the context of severe thrombocytopenia [72–74]. There is no specific treatment for dengue-associated AKI, but a crucial step in patient management is fluid support, maintaining adequate renal perfusion [24]. Great care should be taken with hydration to avoid fluid overload, since intravascular extravasation in dengue is an imminent risk and worsens the prognosis [75]. One factor that contributes to AKI in dengue is rhabdomyolysis, although its true incidence is not well established, but this is another reason why fluid administration is important in dengue and essential to prevent AKI or at least decrease its severity. Since electrolyte disturbances are common, they are also a reason for concern in dengue fever. Special attention should be paid to hyponatremia, the most common hydroelectrolyte disturbance in dengue fever, and fluid replacement should be more tonic in these cases [24]. Severe AKI associated with dengue fever may require dialysis, which is often indicated when patients present with uremia, hypercatabolism, metabolic acidosis, hyperkalemia, and hypervolemia that are refractory to clinical measures. Dengue fever can cause hemodynamic instability, which is why continuous hemodialysis has been indicated for patients with AKI associated with dengue fever in this context [24]. Recently, the Qdenga® vaccine was approved in Brazil for a broad population, aged 4 to 60 years, with an overall efficacy of 80%. It is composed of the four serotypes of the virus and should be administered in two doses, with an interval of 3 months. The previously approved vaccine (Dengvaxia®) can only be used by those who have already had dengue, as individuals without previous contact with the disease have an increased chance of developing severe forms. The CDC recommends the dengue vaccine for children aged 9–16 who have already been infected and who live in endemic areas, and the WHO recommends vaccination for people living in endemic areas, where seroprevalence is greater than 70% [76].

The vaccine is contraindicated in cases of the following:

1. Hypersensitivity to the active substance or any excipient of the composition.
2. Individuals with congenital or acquired immunodeficiency: Individuals receiving immunosuppressive therapies, using corticosteroids (2 mg/kg/day or 20 mg/day of prednisone for 2 weeks or more), or transplant patients, or using chemotherapy.
3. Individuals with symptomatic HIV infection or compromised immune function.
4. Pregnant or breastfeeding women (Pregnancy risk category C).

Dengue vaccine should be postponed in patients with acute febrile illness.

14.13 Zika

It is the infection caused by a virus of the *Flaviviridae* family, first identified in 1947 in the forest region of the same name, in Uganda. The first infection in humans was described in Nigeria a few years later, and for many years, few cases were documented [77]. Transmission occurs through the bite of the *Aedes aegypti mosquito*, and perinatal, sexual, and breast-feeding transmission has also been described between humans.

14.14 Epidemiology

In Brazil, the disease is emerging, with a first peak of incidence documented in 2016, when more than 213,000 probable cases and 11 deaths from the Zika virus were recorded. In 2023, 7292 new probable cases were reported, with no deaths from the disease recorded [7]. In 2024, by the end of March, a total of 1318 cases had been recorded [7]. In addition to affecting adults, Zika has also been associated with an increase in newborns with microcephaly, prompting the declaration of a state of Public Health Emergency of National Importance in Brazil. Between 2015 and 2022, 1857 cases were classified as congenital syndrome by the Zika virus, with a predominance in the Northeast Region [7].

14.15 Clinical and Laboratory Manifestations

The Brazilian Ministry of Health defines a suspected case of Zika as any patient who presents with a pruritic maculopapular rash accompanied by two or more of the following signs and symptoms: fever, conjunctival hyperemia without secretion and pruritus, polyarthralgia, and periarticular edema. In Zika, the symptomatic form usually occurs in 20% of infected individuals. Symptoms appear 2–12 days after the bite by the vector and are characterized by the presence of pruritic maculopapular rash, intermittent fever, nonpurulent conjunctival hyperemia without pruritus, arthralgia, myalgia, and headache. The rash in Zika is usually more severe when compared to the cutaneous manifestations of dengue and chikungunya. The disease has a benign course, and the symptoms usually disappear spontaneously after 3–7 days.

In laboratory tests, Zika virus infection presents with fewer changes in leukocyte and platelet counts compared to dengue and chikungunya. Neurological manifestations in Zika include encephalitis, meningoencephalitis, myelitis, and Guillain-Barré syndrome, among others. Some countries have noted an unusual increase in cases of Guillain-Barré concomitantly with the Zika epidemic. In Brazil, the occurrence of neurological syndrome was confirmed in July 2015, following investigations by the Federal University of Pernambuco, based on the identification of the virus in serum and cerebrospinal fluid samples from six patients with a history of infection with exanthematous disease. Acute disseminated encephalomyelitis occurred in two of these patients and Guillain-Barré syndrome in four.

Specific laboratory diagnosis of Zika is mainly based on the detection of viral RNA from clinical specimens. The viremic period has not been established, but it is believed to be short, which would allow direct detection of the virus up to 4–7 days after the onset of symptoms. In urine, the virus has been detected up to 3 weeks after the onset of symptoms. There is currently no commercially available serology for the detection of antibodies to Zika in Brazil. Currently, only viral isolation and RT-PCR are available, restricted to reference laboratories [2, 14].

14.16 Renal Involvement

Renal involvement in Zika is still not well understood. There is some evidence regarding possible mechanisms that cause kidney disease associated with Zika virus, including persistent elimination of the virus in urine, high susceptibility of glomerular and tubular cells to infection, and release of cytokines associated with inflammation [78]. Zika virus is capable of invading and reproducing in glomerular cells, and the vulnerability of these cells to the virus contributes to its persistence in the urine of infected patients [79, 80]. There is evidence of natural infection by Zika virus in primates in Brazil, and necropsy studies in these animals have identified interstitial nephritis, glomerulonephritis, and tubular injury [81]. An experimental study with different cell types (microglia, fibroblasts, and macrophages) inoculated with Zika virus showed that the cell line present in human kidneys represents a suitable environment for Zika virus replication [82].

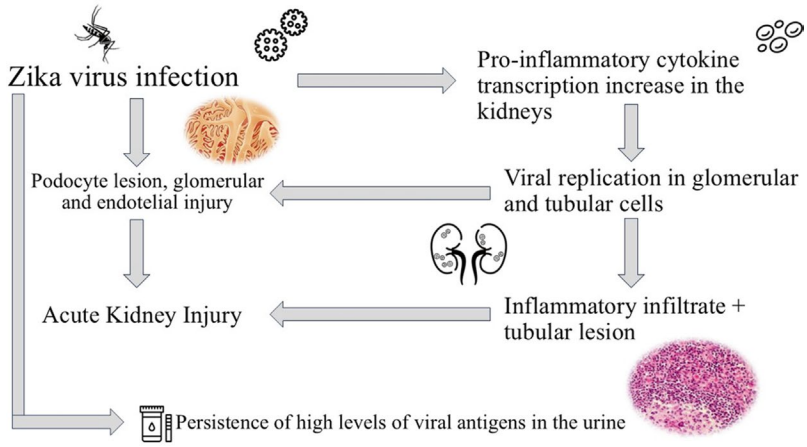


Fig. 14.5 Pathophysiology of renal involvement by the Zika virus

Another study found that high glucose levels in kidney cells reduced viral replication and increased cell survival [79]. Experimental studies have also shown that Zika RNA was detected in glomerular and tubular cells. CD8+ cells were found to be numerically increased in Zika-infected kidneys [83]. New biomarkers of kidney injury have been investigated in Zika, such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) [84]. There is evidence that Zika virus induces inflammation and kidney injury through mechanisms involving the Nod-like receptor 3 (NLRP3) inflammasome and the secretion of interleukin-1β (IL-1β) [84]. Biomarkers of kidney injury were increased in Zika infection and were reduced after blocking the inflammatory process triggered by the infection [84].

In the context of congenital syndrome caused by the Zika virus, Costa Monteiro et al. [85] identified neurogenic bladder in 100% of the 22 patients evaluated. This finding is important since neurogenic bladder, if left untreated, can progress to AKI and CKD. The pathophysiology of renal involvement in Zika is illustrated in Fig. 14.5.

The repercussions of Zika infection in kidney transplant recipients were explored by Nogueira et al. (2017), who reported two cases during an epidemic in São José do Rio Preto, São Paulo, in 2015/2016. AKI was observed in two patients [83, 85, 86].

14.17 Treatment

Like other arboviruses, Zika has no specific treatment, nor antiviral or other medication with proven efficacy. Treatment remains focused on symptom relief [87, 88]. Zika-induced AKI has no specific management recommendations. Current guidelines for the treatment of AKI should be followed.

14.18 Conclusion

Renal involvement in arboviruses is common, ranging from mild and transient loss of renal function to severe renal failure requiring dialysis, which may progress to CKD. The viral infection itself can cause direct renal injury, but other associated factors, such as immune-mediated lesions, and hemodynamic and inflammatory factors, are also important in the pathophysiology of renal injury associated with arboviruses. More recently described diseases, such as chikungunya and Zika, also have the potential to evolve with renal complications, but further studies are still needed to understand all the mechanisms involved. Dengue remains the arbovirus of greatest importance in public health, with an alarming number of cases and consequently with a great potential for complications, including renal involvement, for which monitoring of renal function is essential.

References

1. Paixão ES, Teixeira MG, Rodrigues LC. Zika, chikungunya and dengue: the causes and threats of new and reemerging arboviral diseases. BMJ Glob Health. 2018;3:1–6.
2. Weaver SC, Charlier C, Vasilakis N, Lecuit M. Zika, chikungunya, and other emerging vector-borne viral diseases. Annu Rev Med. 2018;69:395–408.
3. Paz-Bailey G, Adams L, Deen J, Anderson KB, Katzelnick LC. Dengue. Lancet. 2024;403:667–82.
4. Barcellos C, Matos V, Lana RM, Lowe R. Climate change, thermal anomalies, and the recent progression of dengue in Brazil. Sci Rep. 2024;14:5948.
5. Lin PS, Liu WL, Chen CD, Wen TH, Chen CH, Chen LW, et al. Micro-scale urbanization-based risk factors for dengue epidemics. Int J Biometeorol. 2024;68:133–41.
6. Vairo F, Haider N, Kock R, Ntoumi F, Ippolito G, Zumla A. Chikungunya: epidemiology, pathogenesis, clinical features, management, and prevention. Infect Dis Clin N Am. 2019;33:1003–25.
7. Brazil, Ministry of Health. Arbovirus Case Update. Available at: https://www.gov.br/saude/pt-br/assuntos/saude-de-aaz/a/aedes-aegypti/monitoramento-das-arboviroses. Accessed 05/07/2024.
8. Figueiredo LTM. Large outbreaks of chikungunya virus in Brazil reveal uncommon clinical features and fatalities. Rev Soc Bras Med Trop. 2017;50:583–4.
9. Bonifay T, Prince C, Neyra C, Demar M, Rousset D, Kallel H, et al. Atypical and severe manifestations of chikungunya virus infection in French Guiana: a hospital-based study. PLoS One. 2018;13:e0207406.
10. Marques CDL, Duarte ALBP, Ranzolin A, Dantas AT, Cavalcanti NG, Gonçalves RS, et al. Recommendations of the Brazilian Society of Rheumatology for the diagnosis and treatment of chikungunya fever. Part 2 – treatment. Rev Bras Reumatol. 2017;57:S438–51.
11. Vijayan V, Sukumaran S. Chikungunya virus disease: an emerging challenge for the rheumatologist. J Clin Rheumatol. 2016;22:202–11.
12. Rodrigues-Moralez AJ, Cardona-Ospina JA, Villamil-Gómez E, Paniz-Mondolfil AE. How many patients with post-chikungunya chronic inflammatory rheumatism can we expect in the new endemic areas of Latin America? Rheumatol Int. 2015;35:2091–4.
13. Rollé A, Schepers K, Cassadou S, Curlier E, Madeus B, Hermann-Storck C, et al. Severe sepsis and septic shock associated with chikungunya. Emerg Infect Dis. 2016;22:891–4.
14. Sissoko D, Malvy D, Giry C, Delmas G, Paquet C, Gabrie P, Pettinelli F, et al. Outbreak of chikungunya fever in Mayotte, Comoros archipelago, 2005-2006. Trans R Soc Trop Med Hyg. 2008;102:780–6.
15. Centers of Disease Control. Revised diagnostic testing for Zika, chikungunya and dengue viruses; 2016:1–6.
16. Economopoulou A, Dominguez M, Helynck B, Sissoko D, Wichmann O, Quenel P, et al. Atypical chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005–2006 outbreak on Reunion. Epidemiol Infect. 2009;137:534–41.
17. Bruggeman LA. Common mechanisms of viral injury to the kidney. Adv Chronic Kidney Dis. 2019;26:164–70.
18. do Nascimento Costa DM, Machado CE, Neves PD, Brito DJ, Oi S, Barros FH, et al. Chikungunya virus as a trigger for different renal disorders: an exploratory study. J Nephrol. 2022;35:1437–47.
19. Sharp TM, Keating MK, Shieh WJ, Bhatnagar J, Bollweg BC, Levine R, et al. Clinical characteristics, histopathology, and tissue immunolocalization of chikungunya virus antigen in fatal cases. Clin Infect Dis. 2021;73:e345–54.
20. Bower H, El Karsany M, Adam AAAH, Idriss MI, Alzain MA, Alfakiyousif MEA, et al. "Kankasha" in Kassala: A prospective observational cohort study of the clinical characteristics, epidemiology, genetic origin, and chronic impact of the 2018 epidemic of Chikungunya virus infection in Kassala, Sudan. PLoS Negl Trop Dis. 2021;15:e0009387.
21. Danis-Lozano R, Díaz-González EE, Trujillo-Murillo KDC, Caballero-Sosa S, Sepúlveda-Delgado J, Malo-García IR, et al. Clinical characterization of acute and convalescent illness of confirmed chikungunya cases from Chiapas, S. Mexico: a cross sectional study. PLoS One. 2017;12:e0186923.
22. Nkoghe D, Kassa RF, Caron M, Grard G, Mombo I, Bikié B, Paupy C, Becquart P, Bisvigou U, et al. Clinical forms of chikungunya in Gabon, 2010. PLoS Negl Trop Dis. 2012;6:e1517.
23. Staikowsky F, Talarmin F, Grivard P, Souab A, Schuffernecker I, Le Roux K, et al. Prospective study of Chikungunya virus acute infection in the Island of La Réunion during the 2005–2006 outbreak. PLoS One. 2009;4:e7603.
24. Aurore AC, Couderc T, Dueymes JM, Deligny C, Lecuit M, Molinié V, et al. The clinicopathological spectrum of kidney lesions in chikungunya fever: a report of 5 cases with kidney biopsy. Am J Kidney Dis. 2021;78:902–6.
25. Bignardi PR, Pinto GR, Boscarioli MLN, Lima RAA, Delfino VDA. Acute kidney injury associated with dengue virus infection: a review. J Bras Nefrol. 2022;44:232–7.
26. Borgherini G, Poubeau P, Staikowski F, Lory M, Le Moullec N, Becquart JP, et al. Outbreak of chikungunya on Reunion Island: early clinical and laboratory characteristics in 157 adult patients. Clin Infect Dis. 2007;44:1401–7.
27. Lemant J, Boisson V, Winer A, Thibault L, André H, Tixier F, et al. Serious acute chikungunya virus infection requiring intensive care during the Reunion Island outbreak in 2005–2006. Crit Care Med. 2008;36:2536–41.
28. Crosby L, Perreau C, Madeux B, Cossic J, Armand C, Herrmann-Storke C, et al. Severe manifestations of chikungunya virus in critically ill patients during

the 2013-2014 Caribbean outbreak. Int J Infect Dis. 2016;48:78–80.
29. Mahendradas P, Ranganna SK, Shetty R, Balu R, Narayana KM, Babu RB, et al. Ocular manifestations associated with chikungunya. Ophthalmology. 2008;115:287–91.
30. de la Hoz JM, Bayona B, Viloria S, Accini JL, Juan-Vergara HS, Viasus D. Fatal cases of Chikungunya virus infection in Colombia: diagnosis and treatment challenges. J Clin Virol. 2015;69:27–9.
31. Kumar V, Jain R, Kumar A, Nischal N, Jorwal P, Soneja M, Arava S, Wig N. Chikungunya fever presenting as life threatening thrombotic thrombocytopenic purpura. J Assoc Physicians India. 2017;65:96–100.
32. Epelboin L, Bidaud B, Mosnier E, Le Turnier P, Vesin G, Walter G, et al. Fatal case of chikungunya and concomitant thrombotic thrombocytopenic purpura in French Guiana during air flight medical evacuation. J Travel Med. 2017;24:1–3.
33. Hamid A, Dhrolia MF, Qureshi R, Imtiaz S, Ahmad A. Acute kidney injury secondary to rhabdomyolysis: a rare presentation of chikungunya fever. J Coll Physicians Surg Pak. 2018;28:S94–6.
34. Elfert KA, Abdelwahed M, Chi G. Chikungunya virus infection-related rhabdomyolysis: a case report. Cureus. 2019;11:e4036.
35. Solanki BS, Arya SC, Maheshwari P. Chikungunya disease with nephritic presentation. Int J Clin Pract. 2007;61:1941.
36. Arroyo-Ávila M, Cabán A, García-Rivera EJ, Irizarry-Pérez M, Torres H, Gorbea H, Vilá LM. Clinical manifestations associated with peripheral joint involvement in patients with acute chikungunya virus infection. Am J Trop Med Hyg. 2017;96:916–21.
37. Perti T, Lucero-Obusan CA, Schirmer PL, Winters MA, Holodniy M. Chikungunya fever cases identified in the veterans health administration system, 2014. PLoS Negl Trop Dis. 2016;10:e0004630.
38. Freitas ARR, Donalisio MR, Alarcón-Elbal PM. Excess mortality and causes associated with chikungunya, Puerto Rico, 2014-2015. Emerg Infect Dis. 2018;24:2352–5.
39. Frutuoso LCV, Freitas ARR, Cavalcanti LPG, Duarte EC. Estimated mortality rate and leading causes of death among individuals with chikungunya in 2016 and 2017 in Brazil. Rev Soc Bras Med Trop. 2020;53:e20190580.
40. Gupta A, Juneja D, Singh O, Garg SK, Arora V, Deepak D. Clinical profile, intensive care unit course, and outcome of patients admitted to intensive care unit with chikungunya. Indian J Crit Care Med. 2018;22:5–9.
41. Godaert L, Bartholet S, Dorléans F, Najioullah F, Colas S, Fanon JL, et al. Prognostic factors of inhospital death in elderly patients: a time-to-event analysis of a cohort study in Martinique (French West Indies). BMJ Open. 2018;8:e018838.
42. Mesquita LL, Macedo ES, Parente Filho SLA, Beserra FLCN, Girão ES, Ferragut JM, et al. Clinical outcomes of hospitalized patients with chikungunya fever: a retrospective analysis. Asian Pacific J Trop Med. 2021;14:183–6.
43. Pinto JR, Silva Junior GB, Mota RMS, Martins P, Santos AKT, Moura DCN, Pires Neto RJ, Daher EF. Clinical profile and factors associated with hospitalization during a chikungunya epidemic in Ceará, Brazil. Rev Soc Bras Med Trop. 2019;52:e20190167.
44. Silva Junior GB, Jereissati AAR, Pinto JR, Dantas RT, Ramalho JAM, Meneses GC. Chronic kidney disease as an aggravating factor in dengue virus infection. Medicina (Ribeirão). 2024;57(3):e213689.
45. Silva Junior GB, Pinto JR, Mota RMS, Pires Neto RJ, Daher EF. Impact of chronic kidney disease on chikungunya virus infection clinical manifestations and outcome: highlights during an outbreak in northeastern Brazil. Am J Trop Med Hyg. 2018;99:1327–30.
46. Simião AR, Barreto FKA, Oliveira RMAB, Cavalcante JW, Lima Neto AS, Barbosa RB, et al. A major chikungunya epidemic with high mortality in northeastern Brazil. Rev Soc Bras Med Trop. 2019;52:e20190266.
47. Tavares BM, Fernandes PFCBC, Oliveira CMC, Silva SL, Mota UM, Andrade THS, Cunha SF, Girão ES. Chikungunya on kidney transplant recipients: is it the same? Transplantation. 2019;103:441–5.
48. Mercado M, Acosta-Reyes J, Parra E, Guzmán L, Beltrán M, Gasque P, et al. Renal involvement in fatal cases of chikungunya virus infection. J Clin Virol. 2018;103:16–8.
49. Betancur JF, Navarro EP, Bonilla JHB, Cortés AD, Vélez JD, Echeverry A, et al. Catastrophic antiphospholipid syndrome triggered by fulminant chikungunya infection in a patient with systemic lupus erythematosus. Arthritis Rheumatol. 2016;68:1044.
50. Coelho Júnior JL, Petruccelli Israel KC, Machado CE, Muniz MPR, Gatto GC, Barros FHS, et al. Thrombotic microangiopathy associated with arboviral infection: report of 3 cases. PLoS Negl Trop Dis. 2021;15:e0009790.
51. Labadie K, Larcher T, Joubert C, Mannioui A, Dalache B, Brochard P, et al. Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. J Clin Invest. 2010;120:894–906.
52. Hoarau JJ, Bandjee MCJ, Trotot PK, Das T, Li-Pat-Yuen G, Dassa B, et al. Persistent chronic inflammation and infection by chikungunya arthritogenic alphavirus in spite of a robust host immune response. J Immunol. 2010;184:5914–27.
53. Staples JE, Hills S, Powers A. Chikungunya. In: Centers for Disease Control and Prevention, editor. CDC yellow book: health information for international travel. Oxford: Oxford University Press; 2023.
54. Rao S, Erku D, Mahalingan S, Taylor A. Immunogenicity, safety and duration of protection afforded by chikungunya virus vaccines undergoing human clinical trials. J Gen Virol. 2024;105:001965.

55. Khandelwal Vinay G, Patil Virendra C, Amit B, Rahul P. Study of electrolyte disturbances in dengue infected patients. Int J Contemporary Med Res. 2019;6:B5–8.
56. Gurugama P, Jayarajah U, Wanigasuriya K, et al. Renal manifestations of dengue virus infections. J Clin Virol. 2018;101:1–6.
57. Hira HS, Kaur A, Shukla A. Acute neuromuscular weakness associated with dengue infection. J Neurosci Rural Pract. 2012;3:36–9.
58. Vachvanichsanong P, McNeil E. Electrolyte disturbance and kidney dysfunction in dengue viral infection. Southeast Asian J Trop Med Public Health. 2015;46:108–17.
59. Vachvanichsanong P, Thisyakorn U, Thisyakorn C. Dengue hemorrhagic fever and the kidney. Arch Virol. 2016;161:771–8.
60. Jayarajah U, Seneviratne SL, Gurugama P, Wanigasuriya KP. Microalbuminuria and dengue viral infections. Southeast Asian J Trop Med Public Health. 2017;48:938.
61. Eswarappa M, Reddy SB, John MM, Suryadevara S, Madhyashatha RP. Renal manifestations of dengue viral infection. Saudi J Kidney Dis Transpl. 2019;30:394–400.
62. Mallhi TH, Khan AH, Adnan AS, et al. Incidence, characteristics and risk factors of acute kidney injury among dengue patients: a retrospective analysis. PLoS One. 2015;10:e0138465.
63. Lee K, Liu JW, Yang KD. Clinical characteristics, risk factors, and outcomes in adults experiencing dengue hemorrhagic fever complicated with acute renal failure. Am J Trop Med Hyg. 2009;80:651–5.
64. Wiwanitkit V. Immune complex: does it have a role in pathogenesis of renal failure in dengue infection? Ren Fail. 2005;27:803–4.
65. Kuo MC, Lu PL, Chang JM, Lin MY, Tsai JJ, Chen YH, et al. Impact of renal failure on the outcome of dengue viral infection. Clin J Am Soc Nephrol. 2008;3:1350–6.
66. Lee IK, Lee NY, Huang WC, Hsu JC, Tai CH, Yang CH, et al. In-hospital mortality predictors among hospitalized adults and those with chronic kidney disease with dengue. J Microbiol Immunol Infect. 2023;56:996–1006.
67. Silva Junior GB, Jereissati AAR, Pinto JR, Dantas RT, Ramalho JAM, Meneses GC. Chronic kidney disease as an aggravating factor in dengue virus infection: a cross-sectional study. Medicina (Ribeirão Preto). 2024;
68. Ribeiro C, Turani SAD, Miranda SMC, Souza PAM, Penido MGM. Dengue infection in kidney transplant recipients: clinical course and its impact on renal function. J Bras Nefrol. 2022;44:75–83.
69. Bansal SB, Rana A, Gadde A, Jha P, Kotton CN. Dengue infection immediately after kidney transplantation. Transplantation. 2022;106:e354–5.
70. Costa SD, da Silva GB, Jacinto CN, Martiniano LVM, Amaral YS, Paes FJVN, et al. Dengue fever among renal transplant recipients: a series of 10 cases in a tropical country. Am J Trop Med Hyg. 2015;93:394–6.
71. Kala MP, St John AL, Rathore APS. Dengue: update on clinically relevant therapeutic strategies and vaccines. Curr Treat Options Infect Dis. 2023;15:27–52.
72. World Health Organization Regional office for South East Asia. Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever. Revised and expanded ed. New Delhi: World Health Organization South East Asia Regional Office; 2011.
73. Kularatne SA, Dalugama C. Dengue infection: global importance, immunopathology and management. Clin Med (London). 2022;22:9–13.
74. Jasamai M, Yap WB, Sakulpanich A, Jaleel A. Current prevention and potential treatment options for dengue infection. J Pharm Pharm Sci. 2019;22:440–56.
75. Chawla P, Yadav A, Chawla V. Clinical implications and treatment of dengue. Asian Pac J Trop Med. 2014;7:169–78.
76. Vidanapathirana M. Dengue haemorrhagic fever in chronic kidney disease and heart failure: challenges in fluid management. Trop Med Health. 2024;52:33.
77. Kamath V, Aishwarya AB. Dengue vaccines: current status and future perspectives. APIK J Intern Med. 2024;12:1–6.
78. Musso D, Gubler DJ. Zika Virus. Clin Microbiol Rev. 2016;29:487–524.
79. Reslan A, Haddad JG, Koundi LM, Deprès P, Bascands JL, Gadea G. Zika virus growth in human kidney cells is restricted by an elevated glucose level. Int J Mol Sci. 2021;22:2495.
80. Alcendor DJ. Zika virus infection and implications for kidney disease. J Mol Med. 2018;96:1145–51.
81. Burdmann EA. Flaviviruses and kidney diseases. Adv Chronic Kidney Dis. 2019;26:198–206.
82. Terzian ACB, Zini N, Sacchetto L, Rocha RF, Parra MCP, Del Sarto JL, et al. Evidence of natural Zika virus infection in neotropical non-human primates in Brazil. Sci Rep. 2018;8:16034.
83. Tiwari SK, Dang J, Qin Y, Linchinchi G, Bansal V, Rana TM. Zika virus infection reprograms global transcription of host cells to allow sustained infection. Emerg Microbes Infect. 2017;6:e24.
84. Chen J, Yang YF, Chen J, Zhou X, Dong Z, Chen T, et al. Zika virus infects renal proximal tubular epithelial cells with prolonged persistence and cytopathic effects. Emerg Microbes Infect. 2017;6:e77.
85. Liu T, Tang L, Tang H, Pu J, Gong S, Fang D, et al. Zika virus infection induces acute kidney injury through activating NLRP3 Inflammasome via suppressing Bcl-2. Front Immunol. 2019;10:1925.
86. Costa Monteiro LM, Cruz GNO, Fontes JM, et al. Neurogenic bladder findings in patients with congenital Zika syndrome: a novel condition. PLoS One. 2018;13:e0193514.
87. Nogueira ML, Estofolete CF, Terzian AC, et al. Zika virus infection and solid organ transplantation: a new challenge. Am J Transplant. 2017;17:791–5.
88. Ferraris P, Yssel H, Missé D. Zika virus infection: an update. Microbes Infect. 2019;21:353–60.

15 Acute Kidney Injury in Yellow Fever

Cassia Fernanda Estofolete, Rodrigo José Ramalho, Horácio José Ramalho, and Mauricio Lacerda Nogueira

15.1 Introduction

Yellow fever is an acute disease caused by an RNA virus of the genus *Flavivirus* of the Flaviviridae family (from Latin flavus = yellow). The yellow fever virus belongs to the same genus as other main arthropod-borne viruses (arbovirus) that cause human disease, including the Dengue virus, West Nile virus, and Saint Louis encephalitis virus [1].

The yellow fever virus was isolated in 1927, and its complete genome was sequenced in 1985 [2]. The virus is transmitted to humans through the bite of infected female mosquitos and remains in the environment in two epidemiological cycles: the wild cycle, which occurs in nonhuman primates (monkeys) and mosquitoes of the genus *Haemagogus* and *Sabethes*, and the urban cycle, which involves humans and *Aedes aegypti* mosquitoes [3, 4]. Although the cycles are different, from the clinical–pathophysiological point of view, the infection is the same. After a meal of infected blood, the virus migrates to the mosquito's salivary glands and multiplies after an incubation period (extrinsic incubation period = 8–12 weeks). From then on, the female mosquito is able to transmit the virus throughout her life (6–8 weeks) [5].

15.2 Epidemiology

Yellow fever has been responsible for urban outbreaks in the African and South American continents throughout the ages. Recent outbreaks have been described in Brazil, Paraguay and Argentina (2007–2009), Uganda (2010), and Sudan and Ethiopia (2012–2013). Approximately one billion people live in endemic areas and are at risk of the disease in both continents [6]. Since 1942, there have been no records of urban yellow fever in Brazil [7]. In the last two decades, transmissions of the virus were recorded beyond the limits of the area considered to be endemic in Brazil (the Amazon region), in the east-south areas of the country, considered unaffected until then, regions that are densely populated, with unvaccinated populations and infested by vectors [8].

During the period 2016–2017, there was a significant moment of reemergence of the virus in

C. F. Estofolete · R. J. Ramalho
Department of Parasitic and Infectious Diseases, School of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Sao Paulo, Brazil

H. J. Ramalho
Division of Nephrology, Department of Internal Medicine, School of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Sao Paulo, Brazil

M. L. Nogueira (✉)
Department of Parasitic and Infectious Diseases, School of Medicine of Sao Jose do Rio Preto, Sao Jose do Rio Preto, Sao Paulo, Brazil
e-mail: mauricio.nogueira@edu.famerp.br

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_15

Brazil, with dissemination into the Atlantic Forest, accounting for 777 confirmed human cases and 261 deaths. Most cases recorded during the outbreaks occur in males, from rural areas, of economically productive age and who are at risk mainly due to their work activities [9].

Wild yellow fever is characterized by cyclic intervals of 3–7 years, resulting from epizootics in nonhuman primates, coinciding with the appearance of new vulnerable populations [9].

15.3 Clinical Manifestations

Virus susceptibility is universal, and a natural resistance factor to the virus is not known [10]. Human viremia lasts a maximum of 7 days, starting 24–48 h before symptom onset [5].

After an incubation period of 3–6 days, the infection may show a wide spectrum of clinical manifestations, ranging from mild disease, with unspecific symptoms and difficult clinical diagnosis, to severe and fulminant disease, with a lethality of up to 20–50% [11–13].

The variability in the response to the virus is associated with the pathogenic potential of the viral strains and the host's genetic and acquired resistance factors [2]. The yellow fever virus is viscerotropic, with the liver, kidney, spleen, lymph nodes, and heart being the most affected organs [14]. The disease usually occurs in two stages. The first phase includes fever, myalgia, headache, nausea, and vomiting, which may disappear after 3–4 days. Approximately 15% of patients progress to a second, toxemic phase within 24 h of the initial remission, characterized by high fever, chills, jaundice, bleeding episodes, albuminuria, and multiple organ dysfunction, especially hepatorenal failure [6]. At this stage, the Faget sign can be observed, characterized by the occurrence of bradycardia in the presence of high fever.

15.4 Diagnosis

The diagnosis of yellow fever is difficult, especially at symptom onset, as they are nonspecific and may be mistaken for signs of symptoms of other febrile illnesses, such as dengue, Zika, leptospirosis, and viral hepatitis. Specific diagnosis of the infection can be attained by virological methods (virus identification in cell culture, antigens (immunohistochemistry) or viral RNA (RT–PCR, reverse transcription polymerase chain reaction), in blood or tissue and/or serological samples, associated with clinical and epidemiological data. As for serological methods, the detection of yellow fever IgM antibodies (MAC-ELISA) can be made on the fifth day after disease onset; however, it may be susceptible to cross-reactions with other flavivirus antibodies [15].

It is important to recall that yellow fever vaccination also induces IgM formation. Rising antibody titers between a specimen collected in the acute phase and another collected during the convalescent phase, with a fourfold or greater increase, raise the possibility of a recent yellow fever virus infection (hemagglutination inhibition tests in paired samples) [5, 13].

During the infection course, nonspecific biochemical tests may evidence thrombocytopenia, accompanied or not by hemorrhagic episodes, leukopenia, hyperbilirubinemia, especially with increased direct fraction and very high aminotransferase levels, with AST (aspartate aminotransferase) levels exceeding that of ALT (alanine aminotransferase), due to a possible cytopathic effect of the yellow fever virus on the myocardium and skeletal muscles [2, 11]. Urinary sediment may show the presence of bilirubins, red blood cells, and especially proteinuria [16].

15.5 Pathophysiology of Renal Involvement

Acute kidney injury is a complication observed in the severe forms of yellow fever, etiology of which is yet to be completely elucidated. The involvement is a multifactorial one, with an initial prerenal phase and subsequent tubular injury occurrence. The possible mechanisms start from the systemic inflammatory response determined by the viremia, with activation of some circulating inflammatory factors, such as interleukins 12 and 6 [17]. Thus, the main etiology seems to be renal ischemia, associated with disseminated intravascular coagulation and often accompanied

by shock. In an African case series, renal impairment predisposed to increased mortality, mainly in individuals without jaundice or liver disease, prevailing the oliguric aspect associated with uremic complaints [18].

15.6 Kidney Biopsy Findings

Most data on renal biopsy for yellow fever come from animal studies. Using *Rhesus* monkeys, the main findings are acute tubular lesions, including older references identifying the virus in renal tissue [12]. In an experimental mouse model, after the virus inoculation, it was possible to detect them soon in the interstitium [19]; also, in monkeys, 48 h after contact, viral antigens were detected in the glomeruli [12].

Also associated with acute tubular injury, there have been reports of biopsies in humans with eosinophilic degeneration in the tubules, perhaps indicating associated interstitial nephritis. More recently, and contrary to previous findings, an experimental study with monkeys found liver, kidney, and lymph node lesions, but virus antigens were only expressed in liver tissue. These findings corroborate the hypothesis that tissue damage is caused by an indirect effect of viral replication [20].

15.7 Treatment

There is no specific antiviral treatment for yellow fever. Mild cases may have spontaneous resolution, managed with clinical support and symptomatic control. Prevention through immunization is an important factor to reduce the morbidity and mortality of yellow fever. A single dose of the 17-D vaccine is indicated for individuals aged 9 months or older, travelers, or residents of areas at risk of acquiring the infection and can provide lifelong immunity in over 90% of the vaccinated population, after at least 10 days of vaccination. However, because it is an attenuated virus vaccine, there are contraindications: pregnant women, children younger than 6 months, and severe immunodeficiency [21, 22].

Regarding renal support, amidst the excess of severe cases of yellow fever, the following recommendations were suggested for the management of acute renal failure in these patients [23]:

- The nephrologist should be called as soon as possible, and it should be done when creatinine is ≥1.2 mg/dL, or bicarbonate <18 mEq/L, or in the presence of oliguria, with diuresis <0.5 mL/kg/h in 4 h.
- Also, dialysis indications should occur earlier, starting with creatinine >2.0 mg/dL or diuresis <0.5 mL/kg/h in 8 h, with at least one of the following criteria: use of vasoactive drugs, mechanical ventilation, noninvasive ventilation with FiO_2 > 40%, pulmonary congestion, grade II encephalopathy, very positive fluid balance, bleeding episodes, ammonia >100 μmol/L, and bicarbonate <15 mEq/L.

References

1. Vasconcelos P, Travassos da Rosa A, Pinheiro F, et al. Arboviruses pathogenic for man in Brazil. An overview of Arbovirology in Brazil and neighboring countries. Belem: Instituto Evandro Chagas; 1998. p. 72–99.
2. Rice CM, Lenches EM, Eddy SR, et al. Nucleotide sequence of yellow fever virus: implications for flavivirus gene expression and evolution. Science. 1985;229(4715):726–33.
3. Barrett AD, Monath TP. Epidemiology and ecology of yellow fever virus. Adv Virus Res. 2003;61:291–315.
4. Vasconcelos PF, Sperb AF, Monteiro HA, et al. Isolations of yellow fever virus from Haemagogus leucocelaenus in Rio Grande do Sul state, Brazil. Trans R Soc Trop Med Hyg. 2003;97(1):60–2.
5. Brasil, MInistério da Saúde. Febre Amarela. Guia de Vigilância em Saúde. Volume unico. 2nd ed. Brasilia: Ministerio da Saude. Secretaria de Vigilância em Saude. Coordenação Geral de Desenvolvimento da Epidemiologia em Serviços; 2017. 705p.
6. Verma R, Khanna P, Chawla S. Yellow fever vaccine: an effective vaccine for travelers. Hum Vaccin Immunother. 2014;10(1):126–8.
7. Franco O. A história da febre amarela no Brasil. Ministério da Saúde; 1969.
8. Romano AP, Costa ZG, Ramos DG, et al. Yellow fever outbreaks in unvaccinated populations, Brazil, 2008–2009. PLoS Negl Trop Dis. 2014;8(3):e2740.
9. Goldani LZ. Yellow fever outbreak in Brazil, 2017. Braz J Infect Dis. 2017;21(2):123–4.

10. Brès PL. A century of progress in combating yellow fever. Bull World Health Organ. 1986;64(6):775–86.
11. Monath TP. Yellow fever: an update. Lancet Infect Dis. 2001;1(1):11–20.
12. Monath TP, Barrett AD. Pathogenesis and pathophysiology of yellow fever. Adv Virus Res. 2003;60:343–95.
13. Vasconcelos PF. Yellow fever. Rev Soc Bras Med Trop. 2003;36(2):275–93.
14. Monath TP, Vasconcelos PF. Yellow fever. J Clin Virol. 2015;64:160–73.
15. Houghton-Triviño N, Montaña D, Castellanos J. Dengue-yellow fever sera cross-reactivity; challenges for diagnosis. Rev Salud Publica (Bogota). 2008;10(2):299–307.
16. Vasconcelos PF, Costa ZG, Travassos Da Rosa ES, et al. Epidemic of jungle yellow fever in Brazil, 2000: implications of climatic alterations in disease spread. J Med Virol. 2001;65(3):598–604.
17. Lima EQ, Nogueira ML. Viral hemorrhagic fever-induced acute kidney injury. Semin Nephrol. 2008;28(4):409–15.
18. Burdmann EA, Jha V. Acute kidney injury due to tropical infectious diseases and animal venoms: a tale of 2 continents. Kidney Int. 2017;91(5):1033–46.
19. Gershy-Damet GM. Ultrastructural changes caused by yellow fever virus at the level of the kidneys in newborn mice. Arch Inst Pasteur Tunis. 1984;61(1):97–106.
20. Engelmann F, Josset L, Girke T, et al. Pathophysiologic and transcriptomic analyses of viscerotropic yellow fever in a rhesus macaque model. PLoS Negl Trop Dis. 2014;8(11):e3295.
21. Staples JE, Gershman M, Fischer M, (CDC) CfDCaP. Yellow fever vaccine: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep. 2010;59(RR-7):1–27.
22. World Health Organization. Vaccines and vaccination against yellow fever: WHO Position Paper, June 2013–recommendations. Vaccine. 2015;33(1):76–7.
23. Sociedade Brasileira de Nefrologia. Recomendações do manejo de Febre amarela em paciente critico de autoria do grupo de IRA da USP: Sociedade Brasileira de Nefrologia; 2018. Available from https://sbn.org.br/blog/recomendacoes-do-manejo-de-febre-amarela-em-paciente-critico.

16 Hantavirus and the Kidneys

Carlos Ramiro Silva Ramos, Álvaro A. Faccini-Martínez, and Stefan Vilges de Oliveira

16.1 Introduction

Orthohantaviruses, formerly known as hantaviruses, are single-stranded, enveloped, negative-sense RNA viruses whose genome consists of three segments designated as S (small segment), M (medium segment), and L (large segment) [1]. Recently, orthohantaviruses have been reclassified within the *Orthohantavirus* genus, in the family Hantaviridae and the order Bunyavirales, which includes 38 recognized species according to the International Committee on Taxonomy of Viruses (ICTV) [2].

The first cases of hantavirus infections were reported during the Korean War, between 1951 and 1953, where soldiers who came into contact with rodent-infested environments developed fever, myalgia, hemorrhagic manifestations, acute renal failure, and hemodynamic instability [3, 4].

Twenty-five years after this event, the first *Orthohantavirus* was isolated from wild rodents of the species *Apodemus agrarius*. Subsequently, this new agent was called "Hantaan" in reference to the Korean River, where the first cases occurred and the rodents were captured [5].

Soon after that, studies showed that the Korean hemorrhagic fever was not an exclusive disease of that region and was likely to occur in countries such as Russia, China, and Scandinavia [6]. So, it was verified that the Korean hemorrhagic fever was just one of the variants of a group of diseases that manifested by hemorrhage and acute renal failure, which led the World Health Organization to denominate it hemorrhagic fever with renal syndrome (HFRS) [6], a disease that has been linked with five *Orthohantavirus* recognized species: *Orthohantavirus dobravaense*, *Orthohantavirus hantanense*, *Orthohantavirus puumalaense*, *Orthohantavirus seoulense*, and *Orthohantavirus tulaense* [7, 8].

In Brazil, the presence of the *O. seoulense* has been reported since the 1980s [9], with the subsequent description of infections in humans [10] and virus circulation in urban rodent populations of the genus *Rattus* spp. [11].

The first record of human *Orthohantavirus* infection in the Americas was carried out in the United States in the Four Corners region (New

C. R. S. Ramos
Grupo de Enfermedades Infecciosas, Departamento de Microbiología, Facultad de Ciencias, Pontificia Universidad Javeriana, Bogotá, Colombia

Á. A. Faccini-Martínez
Servicio de Infectología, Hospital Militar Central, Bogotá, Colombia

Facultad de Medicina, Universidad Militar Nueva Granada, Bogotá, Colombia

S. V. de Oliveira (✉)
Department of Collective Health, School of Medicine, Federal University of Uberlandia, Uberlandia, Minas Gerais, Brazil
e-mail: stefan@ufu.br

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_16

Mexico, Arizona, Colorado, and Utah) in May 1993, where an outbreak of an acute respiratory disease called hantavirus pulmonary syndrome was reported [12, 13]. In later studies, related to the first cases in South America, an important cardiac involvement was described, which resulted in the change of the nomenclature to hantavirus cardiopulmonary syndrome (HCPS) [14].

In Brazil, the first cases of HCPS were reported in November of the same year from an outbreak that occurred in a rural area of the municipality of Juquitiba, state of São Paulo. These similar cases developed a clinical picture that included respiratory failure, and their serological and histopathological exams confirmed *Orthohantavirus* infection, being recognized as the first outbreak of HCPS in Brazil [15].

16.2 Virology

Morphologically, orthohantaviruses' virions are spherical, ranging from 80 to 120 nanometers. Their genome is composed of three single-stranded negative-sense RNA segments, which are designated as small (S), middle (M), and large (L) segments based on the size of them, which codify the viral polymerase, the nucleocapsid protein, and two viral grycoproteins, respectively [16].

As a result of a widespread geographic distribution of orthohantaviruses, rodent reservoirs, and the disease caused by these viral agents, orthohantaviruses are usually classified in two major groups known as "Old World" and "New World" orthohantaviruses. "Old World" orthohantaviruses (*O. dobravaense*, *O. hantanense*, *O. puumalaense*, *O. seoulense*, and *O. tulaense*) are associated with HFRS, whereas "New World" orthohantaviruses (*Orthohantavirus sinnombreense*, *Orthohantavirus andesense*, *Orthohantavirus chocloense*, and *Orthohantavirus negraense*) cause HCPS [16] (Fig. 16.1).

Orthohantaviruses are grouped by strains that resemble each other according to their morphological, morphogenic, and antigenic properties [17]. Overall, orthohantaviruses have been named according to the geographic region where their first detection was performed [7]. It is also known

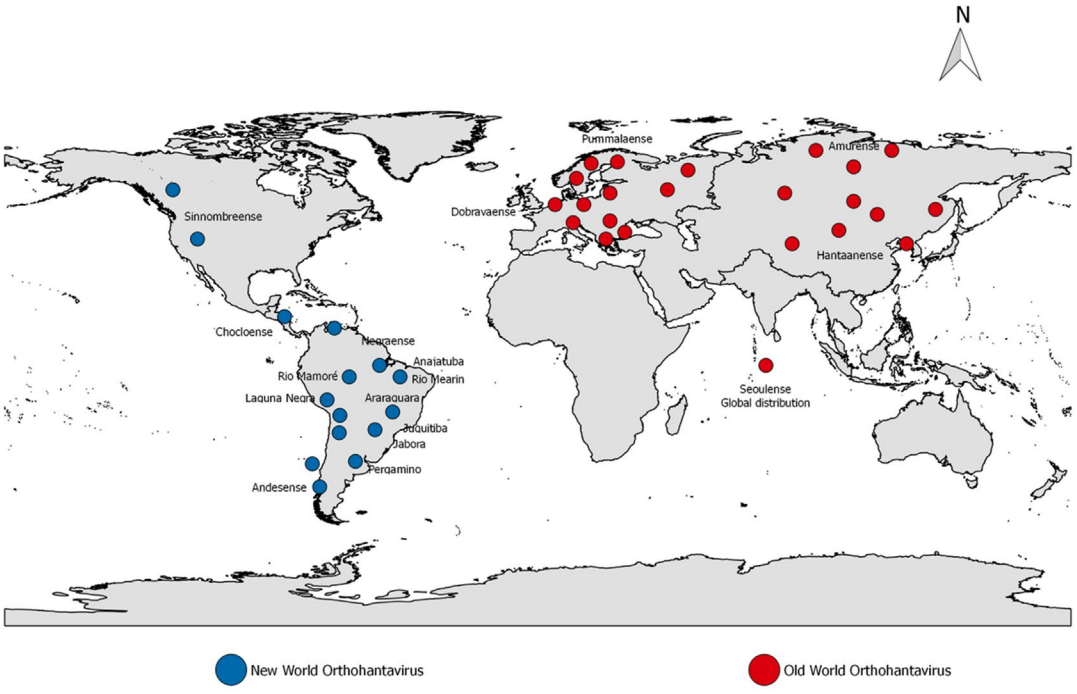


Fig. 16.1 Global geographical distribution of Old World and New World Orthohantavirus variants

that several orthohantaviruses have been associated with less severe clinical pictures [17, 18]; and for some others, their pathogenicity to humans is still unknown, with infections being described only in a few rodent species [17, 19].

16.3 Epidemiology

The HFRS is given different names throughout its distribution area: hemorrhagic nephritis in the former Soviet Union, Songo fever or epidemic hemorrhagic fever in China, Korean hemorrhagic fever in Korea, epidemic nephropathy in Scandinavia, epidemic nephritis or epidemic hemorrhagic fever or Balkan nephritis in Europe, and epidemic hemorrhagic fever in Japan [20].

At first, HFRS was thought to be only present in endemic regions of Eurasia, mainly the eastern part of Russia, the north of Europe, China, and South Korea [21, 22]. Although HFRS is not a compulsory reporting disease in several Asian and European countries, the incidence of this illness worldwide is estimated at 60,000 to 150,000 cases per year [23, 24]. *O. hantanense* and *O. seoulense* have been recognized as the main etiological agents of HFRS in Asia, in addition to *O. dobravaense*, *O. puumalaense*, and *O. seoulense*, which are considered the main etiological agents in Europe [25, 26]. *O. puumalaense* is recognized as the main and most frequent cause of HFRS in Europe, happening all over the continent in regions where *Myodes glareolus* inhabits. Cases due to *O. dobravaense* have only been reported from the Balkan region, despite the fact that the rodent reservoir *Apodemus flavicollis* has a much wider distribution [26, 27]. In Asia, China is considered the country with the highest incidence rate, where between 40% and 50% of all known cases worldwide occur, followed by Russia and South Korea [28]. Due to a geographical expansion and migration of the rodent species *Rattus norvegicus* native from the Old World, *O. seoulense* has been introduced into the American continent and is currently recognized as a cosmopolitan viral agent with a widespread distribution [29]. In the American continent, the presence of the *O. seoulense* has been reported in a few countries such as Argentina, Brazil, Perú, and the United States, demonstrating the importance of this orthohantavirus as the cause of human disease in this part of the world [11, 30–32].

Epidemics of the disease are usually correlated with environmental variations, mainly temperature variations and periods of greater rainfall precipitation, which increases the dynamics of the rodent population; however, cases of HFRS can occur throughout the whole year [16]. Although not mandatory, males are usually at more risk due to the greater number of outdoor activities performed. A mild form of HFRS, formerly known as nephropathia epidemica, is present in the northern region of Europe, among Scandinavian countries such as Finland, Sweden, Denmark, and Norway [33]. Pathogenic strains of orthohantaviruses related with HFRS have been reported in the African continent in few non-rodents hosts such as shrews and chiropterans, but cases of HFRS in this region remain rare and not commonly reported [34, 35]. Transmission of orthohantaviruses, both Old World and New World species, occurs from rodent hosts to humans due to direct or indirect contact; however, for only one species, *O. andesense*, which is associated with HCPS, direct human-to-human transmission has been described [36].

HFRS generally has a low mortality rate, ranging from less than 1% up to 15%, which depends mainly on the viral strain being *O. hantanense* and *O. dobravaense,* more virulent than *O. puumalaense* and *O. seoulense*, contrary to HCPS, which mortality rate can be as high as 40% [37]. Although risk factors have not been totally clarified, some studies have revealed that contact with rodents or their excreta are the main risk factor for Orthohantavirus infection; furthermore, patients older than 70, some genetic characteristics such as the HLA-B8-DR3 haplotype, differences in the immune response, and some habits such smoking, have also been proposed as important risk factors for a more severe outcome and a high mortality rate [16, 38, 39].

16.3.1 Natural History of Hantavirus Infection

The perpetuation of orthohantavirus infection in nature occurs by rodent interactions associated with food competition. At times of food deficit or overcrowding, fights are frequent, which results in contact with saliva or excreted material, thus maintaining the infections in enzootic cycles [40]. Recent studies have also identified other mammals, such as bats, marsupials, and shrews, carrying and hosting different orthohantaviruses; however, the participation of these animals in enzootic and epidemic cycles is not yet well established, but available evidence highly suggests that animals are strong drivers for the maintenance and spread of orthohantaviruses [41].

Orthohantavirus transmission to humans occurs mainly by inhalation of aerosol-dispersed viral particles present in rodent droppings and saliva. Rarely, contagion can also occur through the bite of infected animals, inoculation into the skin or mucous membranes with solution of continuity, or ingestion of water or food contaminated by the virus [3, 42].

Despite the severity of some infections due to a few *Orthohantavirus* species, oligosymptomatic and even asymptomatic cases of human hantavirus infection are known to occur. These cases are confirmed due to the presence of hantavirus antibodies in the general population, detected in serological surveys, including in individuals with no epidemiological history [43].

The incubation period of the disease may vary from a few days to 2 months. The minimum period recorded was 3 days, and the maximum period recorded was 60 days. Most cases show the first signs of the disease around 2 weeks after the exposure. The median duration of the disease from symptom onset to cure or death is 5 and 13 days, respectively [42, 44].

16.4 HFRS Clinical Manifestations

Both HFRS and HCPS can share similar features such as a strong inflammatory process, vascular endothelium cells damage, and multisystem damage with renal and respiratory failure, despite being two different clinical entities [14, 45, 46].

Although the clinical picture of HFRS depends on some typical pathophysiological features such as the development of alteration of vascular permeability, coagulation dysregulation, and kidney injury, the main determinant of the clinical course and the disease severity depends on the virus species and the host immune response, being a highly variable clinical entity [37].

HFRS usually develops after an incubation period that lasts from 2 to 6 weeks, during which subclinical or oligosymptomatic infections are not uncommon. Clinically, HFRS is characterized by the development of sudden fever along with several nonspecific symptoms (e.g., chills, myalgias, nausea). Classically, HFRS can be divided into five clinical phases: febrile, hypotensive, oliguric, diuretic, and convalescent; however, in several cases, these periods may overlap, patients do not always follow a typical clinical course, and in mild cases, these phases do not even occur [37, 47].

When the disease is clinically symptomatic, a first febrile phase develops, which usually lasts about 3–7 days, in which hypotension is usually frequent due to vascular leakage. Coagulation abnormalities can occur, such as thrombocytopenia and hemorrhagic diathesis, being the presence of diffuse cutaneous hyperemia affecting the face, neck, and upper chest, and petechiae on the soft palate and armpits being the most common physical findings. Bleeding is more frequent in severe HFRS cases, usually caused by *O. hantanense* and *O. dobravaense*, which includes epistaxis, menorrhagia, metrorrhagia, and gastrointestinal bleeding; however, fatal outcomes due to bleeding are rare. The liver can be palpated in a significant number of cases; liver impairment is more common in infections caused by *O. seoulense*. Many patients recover slowly from this phase, but some develop hypotension and shock, which usually occur before the sixth day after symptoms started. The blood pressure drop may be mild, but some patients develop refractory shock, which requires the use of vasoactive drugs. Sudden albuminuria can also be frequent at the end of the fever phase [37, 44].

Then, the hypotensive phase can occur, which lasts from several hours to a couple of days, in which hemodynamic and bleeding complications can also occur, and one-third of cases usually have a fatal outcome due to hypotensive shock. During this phase, several hemodynamics alterations are usually developed, including the presence of thrombocytopenia <70,000/mm [3], proteinuria >3000 mg/day, decreased in the urinary density, hemoconcentration (hematocrit >50%), and leukocytosis, sometimes with leukemoid reaction, the most common features [37, 44].

Subsequently, an oliguric phase is developed in half of HFRS cases, which usually lasts from 3 to 7 days, and is usually associated with hypertension, pulmonary edema, and complications of renal insufficiency; this phase is associated with about half of the fatal cases and patients often requires hemodialysis. Bleeding is more common during this phase and can be observed in the conjunctiva, skin and mucosa, digestive tract, and central nervous system; microscopic hematuria is also frequent at this stage. Ocular symptoms such as blurred vision can occur and are linked to a thickening of the lens leading to transient myopia, which is more common in *O. puumalaense* infections. Renal function deteriorates, usually 24 h after hypotension, with the onset of oliguria or even anuria, which requires the use of dialysis methods due to acute renal failure, which is more common in cases due to *O. dobravaense*. Laboratory finding during this phase includes proteinuria, hematuria, increased creatinine and blood urea nitrogen, decreased plasma albumin concentration, elevated hemoglobin concentration, and thrombocytopenia. Inflammation markers such as C reactive protein and interleukin 6 are also elevated. Elevated liver transaminases, lactate dehydrogenase, and leukocyte counts are also frequent. Cardiopulmonary involvement with respiratory failure, relative bradycardia, and shock might also occur within this phase. Patients with HFRS mostly die from shock, complications of renal insufficiency, and multiorgan failure. Among 30–50% of HFRS patients are hospitalized due to severe symptoms present during this phase. It should be clinically differentiated from leptospirosis and other viral hemorrhagic fevers that occur in the same areas of occurrence of hantavirus infections. Studies in Europe have indicated that smoking is a risk factor for developing acute renal failure and a severe disease in patients infected with *O. puumalaense* [37, 44, 48].

Those patients who survive develop a diuretic phase, which usually lasts from 2 to 3 weeks, with the production of a large daily urine output. The recovery from this moment onward can be rapid, with the onset of intense diuresis of above 3 liters per day; also, hydroelectrolytic disorders, such as hypokalemia, hyponatremia, and hyperphosphatemia, can occur, as well as episodes of arterial hypertension. Fatal outcomes can also occur within this phase due to shock [37, 44].

Finally, a convalescent phase can be developed, which usually lasts for several months, as long as 3–6 months in which the patient is in a period of slow recovery. Although uncommon, some patients can have renal sequelae in the first months or years after the convalescence phase, such as increased glomerular filtration rate and proteinuria. However, such sequelae tend to disappear over time, without evidence of chronic kidney disease or end-stage renal failure [44, 49].

16.5 Diagnosis

Orthohantavirus infection should be suspected in any patient with an acute undifferentiated febrile illness (AUFI) with a marked decrease in platelet count who resides in an endemic area or has recently traveled to an endemic region; the presence of proteinuria and hematuria supports the clinical suspicion and can also help to reach out HFRS diagnosis [44].

Serology is the most widely used diagnostic method for the detection of *Orthohantavirus* infection. Laboratory diagnosis is commonly performed by the enzyme-linked immunosorbent assay (ELISA), which aims to detect mainly the IgM antibodies associated with recent infection. Such a diagnosis is possible even in the acute phase of the disease because antibodies anti-orthohantaviruses appear with the onset of clini-

cal manifestations [50, 51]. Molecular methods such as reverse transcription polymerase chain reaction (RT-PCR) are also useful and practical for diagnosis of *Orthohantavirus* infection, since the viral RNA can be detected within clinical samples [51].

16.5.1 Laboratory Diagnosis

The serological standard method for confirmation of *Orthohantavirus* infection is enzyme-linked immunosorbent assay (ELISA). IgM anti-orthohantaviruses antibodies are usually present at onset of the febrile phase, and approximately 95% of HCPS patients have detectable IgM antibodies in a serum sample collected when symptoms begin; thus, it is an effective method for the diagnosis of *Orthohantavirus* infection [52–54]. Detection of IgG anti-orthohantaviruses antibodies can also be performed; however, these are mostly used for epidemiological and seroprevalence studies rather than for diagnosis, which can detect previous exposure to orthohantaviruses [50, 51].

Immunochromatographic IgM assays prepared with the proteins of the nucleocapsid can also be used for the diagnosis of HFRS caused by a specific *Orthohantavirus* or using a combined format for the diagnosis of more than one virus. These assays have demonstrated to have a greater performance compared with ELISA IgM assays. Furthermore, immunochromatographic tests for Old World orthohantaviruses can also be useful for New World orthohantaviruses; however, in order to reduce false positive results, specific ELISA tests should be performed for confirmation [55–57].

Immunohistochemistry techniques can also be used; however, they are usually performed for retrospective and postmortem diagnosis, when it was not possible to perform the serological diagnosis when the patient was still alive [51].

Reverse transcription-polymerase chain reaction (RT-PCR) is a sensitive and specific method, highly useful not only for diagnosis but also for identifying specific species and genotypes when epidemiological studies are performed. RT-PCR is usually designed to detect the S segment of the virus [58–60]. Buffy coat has proven to be a better sample than plasma since the viral loads in this sample are higher for up to 2 weeks before clinical manifestations begin and circulating antibodies are detectable [60, 61].

16.5.2 Nonspecific Laboratory Diagnosis

Although not specific, HFRS can be suspected with the help of some laboratory findings, such as significant leukocytosis with thrombocytopenia and high or normal hematocrit level; liver enzymes, blood urea nitrogen, and serum creatinine can also be elevated; hyponatremia, hyperkalemia and hyperphosphatemia can be evidenced when the patient is in the oliguric phase; complement levels can be reduced, mainly the C3 component; the presence of prolonged prothrombin time, activated partial thromboplastin clotting time, and bleeding time may be associated with a more severe condition; fibrin and fibrinogen degradation products can be elevated; and although not common, serum amylase and lipase can also be elevated [45, 62].

The presence of macroscopic or even microscopic hematuria or proteinuria in the urinalysis test may represent a more serious disease with acute kidney injury, mainly when it is associated with thrombocytopenia and decreased urine output. In the oliguric phase, elevated creatinine and decreased glomerular filtration rate can be evidenced. When anuria is developed, electrolyte imbalances can also be evidenced, such as elevated levels of potassium and phosphorus in the bloodstream [45, 63].

16.5.3 Differential Diagnosis

HFRS needs to be differentiated with other infectious and noninfectious febrile illnesses, mainly during the febrile phase, considering principally those diseases that are endemic in the geographic region where cases of HFRS have been detected. Infectious diseases that must be differentiated

include leptospirosis, rickettsiosis, influenza and parainfluenza virus infection, dengue fever, yellow fever, Rift Valley fever, Crimean-Congo hemorrhagic fever, Coxsackie virus infection, Adenovirus infection, Lassa fever, trichinellosis, malaria, atypical pneumonia, septicemia, typhoid fever, histoplasmosis, and pneumocystosis. In pregnant women, HFRS needs to be differentiated from HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome [44, 51, 64].

Other noninfectious diseases that could simulate HFRS and must be differentiated include acute abdomen of variable etiology, acute respiratory distress syndrome (ARDS), acute pulmonary edema, interstitial pneumonia by collagen disease such as systemic lupus erythematosus or rheumatoid arthritis, and chronic obstructive bronchopulmonary disease (COBPD) [44, 65].

16.6 General Pathophysiology and Kidney Impairment

The viral infection begins when orthohantaviruses attach to integrin and complement receptors of endothelial cells of the lung microvasculature through their glycoproteins, and the viruses get into the host cell through endocytosis. Membrane fusion is mediated through a pH-dependent step, and ribonucleic proteins are liberated in the cytoplasm. Viral transcription mainly occurs in the endoplasmic reticulum, Golgi intermediate compartment, where the viral RNA-dependent RNA polymerase performs the transcription and replication of the virus due to its endonuclease, replicase and transcriptase activities. The glycoprotein precursor is produced on the endoplasmic reticulum membrane, and the assembly process starts with the transfer of G1 and G2 from the endothelium reticulum to the Golgi complex in case of Old World orthohantaviruses, where they congregate. New replicated virions are expelled through exocytosis [1, 37, 66].

After viral replication, the virus disseminates through the lymphatic route to other organs and tissues, and when reaching the renal microvasculature, capillary leakage is produced in the renal glomeruli and the tubular cells, which are responsible for the primary clinical manifestation of the renal dysfunction. However, most of the pathogenic mechanisms of orthohantavirus infection are triggered by an autoimmune response, since orthohantaviruses do not induce increased capillary permeability only by themselves [66, 67]. Orthohantavirus infection is recognized as an infectious vasculitis since the small vessel endothelium is the main target for these viruses. The disease severity increases after the immune response is triggered, producing abnormal coagulation with platelet aggregation, resulting in consumptive coagulopathy and complement activation, which can result in disseminated intravascular coagulation and thrombosis [48, 66].

The main pathophysiological damages associated with HFRS are caused by a hyperreactive immune response to orthohantaviruses. Several cytokines, such as IL-6, IL-18, IFN-γ, and TNF-α, have been associated with a severe course of the disease; the complement pathway activation also plays an important role in the pathogenesis of the disease; and vascular endothelial growth factors are considered the main mediators of the increased vascular permeability [45, 68, 69]. T lymphocytes are one of the principal cells that are activated very early during orthohantavirus infection, which also increases the number of other immune cells, such as monocytes, neutrophils, B lymphocytes, and CD8 cytotoxic T lymphocytes. Neutralizing antibodies are thought to have an important role in the defense against orthohantaviruses [37, 70].

In the kidneys, orthohantaviruses mainly infect podocytes, glomerular endothelial cells, and tubular epithelial cells, in which they bind and enter through αvβ1-integrins and components of the complement system, such as CD55 and GC1qR/p32 [25]. Under basal conditions, β-integrins contribute to the regulation of vascular integrity, endothelial cell permeability, restriction of vascular endothelial growth factors, and platelet functions [45, 48]. The viral infection inhibits normal regulation of β-integrins, inducing an increased endothelial cell response and producing a significant increase in vascular per-

meability. Additionally, there is redistribution and a decrease in intercellular junctions, which explains the proteinuria, which can be present during the acute phase of the disease; urinary loss of low molecular weight proteins, such as α1 and β2 microglobulins, suggests that tubular involvement also contributes to proteinuria [37, 45, 48]. Increased vascular permeability in different organs and tissues, including kidneys, may explain the typical characteristics of orthohantavirus infection, such as hemoconcentration, hypotension, shock, among others [37, 45, 48]. A greater renal damage is triggered during the course of HFRS, contrary to HCPS in which the renal system can also be affected, but with a great pulmonary and cardiac involvement; however, to date, little is known about the differences between Old and New World orthohantaviruses and why they target some organs more severely [69].

16.7 General Considerations and Findings on Renal Biopsy

Orthohantavirus infections usually have little histopathological evidence of cell damage, and no pathognomonic lesions are found. The lungs are the most frequently injured organs in HCPS, where pulmonary edema is described, with discrete hyaline membrane, interstitial lymphocyte infiltrate, and activated macrophages [71–73].

Renal *Orthohantavirus* infection is typically described as acute tubulointerstitial nephritis. Findings in the histopathology include cell infiltrates (leukocytes, plasma cells, monocytes, macrophages, polymorphonuclear cells), edema and interstitial hemorrhages, medullary hemorrhages, alterations in the tubular epithelium and lumen, generalized capillary damage with intratubular alterations and interstitial edema, and sporadically, glomerular involvement with hypercellularity and mesangial expansion [45, 71, 74] (Fig. 16.2). The severity of acute renal failure is due to the level of tubulointerstitial and glomerular damage; however, glomerulonephritis is a rare consequence of *Orthohantavirus* infection [71, 74].

During a study performed in France, renal histopathological findings were characterized among 17 patients diagnosed with HFRS secondary to *O. puumalaense* [75], in which interstitial hemorrhage and acute tubular necrosis were commonly described, but interestingly, interstitial nephritis was not frequent; moreover, renal microvascular inflammation with the presence of T lymphocytes and macrophages was observed, with cortical peritubular capillaritis and in the medullary portion of the vasa recta [74, 75].

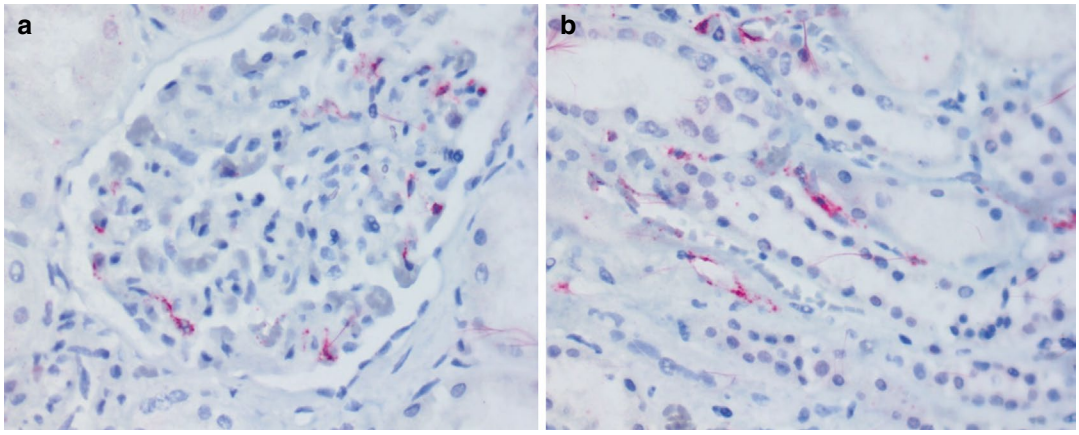


Fig. 16.2 (**a**) Endothelial cells of glomerular capillaries containing hantavirus antigens detected by the immunohistochemical technique. (**b**) Endothelial cells containing hantavirus antigens detected by immunohistochemical technique in the renal medullary capillaries. A and B—mouse monoclonal A1C5 for hantavirus, Abcam, alkaline phosphatase conjugated polymer, and fast red substrate, counterstained with hematoxylin; 40X. (Courtesy of Silvia D'Andretta Iglezias, Pathologist at the Instituto Adolfo Lutz, Pathological Anatomy Center, São Paulo)

16.8 Treatment

To date, neither HFRS nor HCPS has a specific approved antiviral treatment, and confirmed and suspected cases need to be treated using supportive measures to maintain the patient's physiological status. Those patients with a severe form of the disease must be transferred urgently to an intensive care unit for careful observations [76]. Fluid maintenance and electrolyte balance based on the patient's fluid status, diuresis, and renal function need to be carefully monitored to prevent unfortunate outcomes. In patients with renal insufficiency, dialysis is necessary; and when a significant bleeding occurs with marked thrombocytopenia, platelet concentrate infusions may be highly helpful [77].

Symptomatic treatment can be administered to patients with mild forms of the disease. When necessary, hydration should be carefully provided to avoid volume overload. Strict control of vital data regarding hemodynamic and ventilatory parameters is required to prevent worsening the patient's condition [76].

In those patients with a severe form of the disease, careful intravenous (IV) fluid infusion is recommended, which must be administered carefully to prevent edema development. Adequate management of fluid balance is an important parameter, which requires control of diuresis, bladder catheterization (not mandatory), and renal function. The volume of IV fluids should be sufficient to maintain the preload and ensure adequate renal plasma flow, maintaining a negative or at least zero fluid balance, without producing edema with a maximum volume of 2500 mL in 24 h for adults. Colloidal and plasma solutions may be employed to achieve a negative or zero fluid balance, sufficient to optimize volemia with central venous pressure <6 cm of fluid and maintain good renal flow. In critically ill patients, central venous access is recommended for preload evaluation and monitoring [76].

Vasoactive cardiotonic drugs, such as norepinephrine at a dose of 0.01–1 μg/kg/min, should be administered to maintain hemodynamic conditions and prevent shock. As a second option, dopamine (2–5 μg/kg/min at dopa dose and 5–10 μg/kg/min at beta dose) can be used continuously. Dobutamine at a dose of 8–15 μg/kg/min should be reserved for refractory cases, in combination with another vasoactive drug when severe hypotension or decreased myocardial performance are observed. When not available, other drugs such as adrenaline and phenylephrine can be used as second-choice therapy [76].

In patients with a severe illness, continuous hemodynamic, ventilatory support, and monitoring are required. Oxygen supply should be administered, ensuring arterial saturation of at least 90% in patients who require it. In cases of mild respiratory failure and stable clinical status, early noninvasive ventilation (bilevel positive airway pressure ventilatory support [BIPAP)/continuous positive airway pressure (CPAP)] may be applied. Patients with more accentuated respiratory distress and O_2 saturation <80%, with signs of respiratory fatigue and chest X-ray compatible with severe acute respiratory distress syndrome, should be assisted with invasive mechanical ventilatory assistance. In this condition, PEEP (positive end-expiratory pressure) between 10 and 18 cm [3] of H_2O should be established in an attempt to reduce edema and the risk of pulmonary bleeding. In mechanical respiratory assistance, the controlled pressure mode is used, adjusting the inspiratory pressure so that the inspiratory peak of 35–40 cm [3] is not exceeded, maintaining an adequate CO_2 exchange. In the controlled volume modality, whenever possible, the tidal volume can be adjusted to 5–7 mL/kg of body weight, in an attempt to control with FiO_2 <60%, varying as necessary [76].

In cases of HFRS, in addition to the hemodynamic support, the maintenance of the hydroelectrolytic balance is crucial. The use of nephrotoxic agents, such as nonsteroidal anti-inflammatory drugs, should be avoided [45, 76, 78]. In patients with acute renal failure with hemodynamic stability, intermittent hemodialysis is usually the first-choice procedure. In critically ill patients with multiorgan dysfunction syndrome, pulmonary edema, fluid overload, hydroelectrolytic disorders, encephalopathy, and acute renal failure, continuous renal replacement therapy is highly indicated [45, 76, 78].

Antiviral drugs such as ribavirin and favipiravir have been evaluated against *Orthohantavirus* infection. In vitro and in vivo studies have shown that ribavirin is effective against some orthohantaviruses; infected suckling mice that received 50 mg of ribavirin/kg/day survived longer than control specimens [79]; however, clinical studies among patients with HFRS showed a reduction of severity, but insufficient enough to demonstrate effectiveness for HFRS treatment [80]. Favipiravir has been tested against a few New World orthohantaviruses, in vitro studies have shown that *O. sinnombreense* and *O. andesense* are inhibited by favipiravir, increasing the survival of hamsters infected with these viruses [81]. Favipiravir has not been evaluated against Old World orthohantaviruses.

Other drugs such as lactoferrin, an iron-binding glycoprotein, have been shown to be effective alone and in combination with ribavirin, with which it has synergistic activity, against *Orthohantavirus* infection [82]. Also, vandetanib, a tyrosine kinase inhibitor, has been developed which targets the stimulation of vascular endothelial growth factor-receptor 2 and, thus, decreases the vascular permeability and the progression to a serious illness, but severe adverse events such as dermatological and cardiovascular effects can occur [83]. Finally, the effectiveness and security of immunotherapy employing human immune serum as an alternative treatment against New World orthohantavirus infection has also been evaluated, showing that it can prevent fatality [84].

16.9 Prevention and Control

Contact with rodents or their excreta represent the main risk factor for *Orthohantavirus* infection. Therefore, rodent population control represents the most important prevention measure; in that way, rodent food sources should be eliminated inside and around houses, entry points must be blocked, and potential nesting sites should be removed [3, 77]. Rodent-infested spaces should be ventilated before entering, or use personal protective equipment to prevent infectious particle inhalation [85].

Although an *Orthohantavirus* vaccine has not been approved yet, a few strategies and approaches have been made. First-generation vaccines include inactivated virus immunizations which have been tested in China and Korea between 1950 and 2007 against *O. hantanense* and *O. seoulense*, for which high rates of specific IgM and IgG neutralizing antibodies are produced, which can last for 33 months after vaccination, with high peak levels 3 months after vaccination [86]. A formalin-inactivated *O. hantanense* vaccine (Hantavax) is used in Korea in a three-dose schedule (0, 1 and 13 months), which generate a 2-year immunogenicity and booster effect [87].

Second-generation vaccines include *Orthohantavirus*-like particles and recombinant protein vaccines. The first one developed high neutralizing antibody levels and long-lasting protection of about 6 months [88, 89]. On the other hand, recombinant protein (viral) vaccines have also been developed, which use the nucleocapsid protein and the viral glycoproteins as antigens; those vaccines that use the nucleocapsid protein as an antigen have showed to be highly cross-reactive among several orthohantaviruses [88, 89].

Third-generation vaccines include recombinant vector and nucleic acid-based molecular vaccines. Recombinant vector vaccines based on the M and S regions of *O. hantanense* cDNA inserted in vaccinia virions effectively protected hamsters from *O. hantanense* and *O. seoulense* but failed to produce a high level of neutralizing antibodies in clinical trials. DNA vaccines containing either M or S gene segment of *O. hantanense* or *O. seoulense* have been produced, which protected hamsters and monkeys against *O. hantanense*, *O. seoulense* and *O. dobravaense* [90, 91]; also *O. hantanense* and *O. puumalaense* M segment DNA vaccines were produced, which generated neutralizing antibodies against both viruses in more than 50% of volunteers employing an intramuscular electroporation delivery technique [92].

16.10 Epidemiological Surveillance Actions

Cases of *Orthohantavirus* infections should be compulsorily notified to the Brazilian Ministry of Health, and it is the obligation of health professionals to immediately report suspected cases. Every case of *Orthohantavirus* infection should be investigated immediately after the notification, assessing the need for relevant control measures [93].

The confirmatory diagnosis of an *Orthohantavirus* infection case should consider the clinical, epidemiological, and laboratory diagnosis; thus, the Brazilian Ministry of Health adopts the following case definitions [93]:

Suspected Case

- Patient with fever >38 °C, myalgia and headache, and signs/symptoms of acute respiratory failure of undetermined etiology in the first week of the disease
- Patient with acute illness, with acute respiratory failure, progressing to death in the first week of the disease or
- Patient with fever >38 °C, myalgia, and headache who has been exposed to a risk situation,∗ related or not to laboratory-confirmed cases

∗Risk factors for *Orthohantavirus* infection [93]

Exposure to at-risk activities for hantavirus infection within 60 days prior to symptom onset: (a) deforestation, tree cutting, and logging; (b) plowing, planting, or harvesting in the field; (c) grain transportation, storage, and milling; (d) storing or handling bales of hay, firewood, or similar; (e) cleaning barns or other similar constructions (greenhouses, granaries, storerooms, and silos); (f) cleaning of agricultural machinery; (g) entering, resting, and/or cleaning of residences or any other type of construction, occupied or not, regardless of the time; and (h) exposure to rural and/or wild environment in professional or leisure activities (hunting, fishing, ecotourism, military training, and scientific research).

Existence of population of wild rodents and/or favorable environmental conditions for its establishment, in places frequented by the patient: (a) direct contact and/or presence of live/dead wild rodents or their excreta/traces (stool, urine, and/or urine smell); (b) presence of *Brachiaria* sp. grass; (c) abandoned fields, unoccupied grasslands; (d) change in the agricultural profile or other episodic natural phenomena that alter the availability of food (grains) for wild rodents, such as fruiting of native trees and flowering of bamboo plants [94]; (e) environmental factors that cause the displacement of rodents to the homes or surrounding human dwellings, such as deforestation, burning, floods, among others; and (f) climate changes and episodic natural phenomena with direct effects on the rodent population.

It is noteworthy that in Brazil, although HCPS is the predominant clinical pattern, there are studies that confirm the circulation of the *O. seoulense* in both humans and urban rodents of the genus *Rattus*, in addition to the description of cases with manifestations compatible with HFRS, clinically indistinguishable, and probably underdiagnosed in the presence of suspected cases of leptospirosis [9–11, 95]. Therefore, infections caused by this virus should be suspected in patients with acute febrile syndrome, thrombocytopenia and proteinuria, or acute renal failure, with exposure to urban rodents [96].

Confirmed Case

According to Laboratory Criteria

- Suspected case with the following laboratory test results:
  - Reactive serology for *Orthohantavirus*-specific serum antibodies of the IgM class
  - Positive tissue immunohistochemistry (identification of hantavirus-specific antigens)
  - Positive RT-PCR for *Orthohantavirus*

According to Epidemiological Clinical Criteria

- Individual with a clinical condition of acute respiratory failure or acute renal failure who

has died, without collection of specimens for specific tests, and who has been to areas of known hantavirus transmission or been exposed to the same at-risk situation as laboratory-confirmed patients in the last 60 days

Discarded Case

- Any suspected case that, during the investigation, has a laboratory-confirmed diagnosis of another disease or does not meet the previously defined confirmation criteria

In parallel with the investigation of the human case, environmental surveillance activities are triggered, called eco-epidemiological surveillance actions, which imply activities at the probable site of infection, aimed at identifying the prevalent rodent species and, among them, determining the probable reservoir and the circulating *Orthohantavirus* [93, 97]. These studies aim to expand the knowledge about the epidemiological behavior of *Orthohantavirus* infections in a given area, contribute to the knowledge about the natural history of the disease, and assist decision-making regarding prevention and control actions [93].

Serological studies on wild rodents have been carried out since 1993, when the first cases of *Orthohantavirus* were detected. Due to these studies, the identification of new *Orthohantavirus* reservoirs, new genera and species of wild rodents, and new variants has been systematically performed [93].

Serological surveys in human populations may also support the assessment and recognition of transmission areas, and studies carried out in Brazil have reported a prevalence of between 2% and 18%, depending on the study site and age group investigated. The most interesting data from surveys performed in Brazil are from Badra et al. [98], who retrospectively analyzed (1987–1990) samples from a blood bank of residents of the municipality of Cacia dos Coqueiros—state of São Paulo—and found a prevalence rate of around 5%, even before the confirmation of the first cases of the disease in the Americas.

16.11 Take-Home Message

- *Orthohantavirus* infection should be suspected in any patient with an acute undifferentiated febrile illness (AUFI) with a marked decrease in platelet count who resides in an endemic area or has recently traveled to an endemic region.
- HFRS needs to be differentiated from other infectious and noninfectious febrile illnesses, especially during the febrile phase, considering mainly those diseases that are endemic in the geographic region where cases of HFRS were detected.
- Patients with a severe form of the disease must be urgently transferred to an intensive care unit for careful observation. Fluid maintenance and electrolyte balance based on the patient's fluid status, diuresis, and renal function need to be carefully monitored to avoid unfortunate outcomes.
- Contact with rodents or their excreta represents the main risk factor for *Orthohantavirus* infection. Therefore, control and management of the rodent population represents the most important prevention measure; rodent food sources must be eliminated in and around homes, entry points must be blocked, and potential nesting sites must be removed. Rodent-infested spaces should be ventilated before entering, or use personal protective equipment to prevent inhalation of infectious particles.

References

1. Munir N, Jahangeer M, Hussain S, Mahmood Z, Ashiq M, Ehsan F, Akram M, Ali Shah SM, Riaz M, Sana A. Hantavirus diseases pathophysiology, their diagnostic strategies and therapeutic approaches: a review. Clin Exp Pharmacol Physiol. 2021;48(1):20–34. https://doi.org/10.1111/1440-1681.13403.
2. Zerbini FM, Siddell SG, Lefkowitz EJ, Mushegian AR, Adriaenssens EM, Alfenas-Zerbini P, Dempsey DM, Dutilh BE, García ML, Hendrickson RC, Junglen S, Krupovic M, Kuhn JH, Lambert AJ, Łobocka M, Oksanen HM, Robertson DL, Rubino L, Sabanadzovic S, Simmonds P, Smith DB, Suzuki N, Van Doorslaer K, Vandamme AM, Varsani A. Changes

to virus taxonomy and the ICTV statutes ratified by the international committee on taxonomy of viruses (2023). Arch Virol. 2023;168(7):175. https://doi.org/10.1007/s00705-023-05797-4.
3. Krüger DH, Ulrich R, Lundkvist AA. Hantavirus infections and their prevention. Microbes Infect. 2001;3(13):1129–44. https://doi.org/10.1016/s1286-4579(01)01474-5.
4. Lee HW, Lee PW, Johnson KM. Isolation of the etiologic agent of Korean hemorrhagic fever. J Infect Dis. 1978;137(3):298–308. https://doi.org/10.1093/infdis/137.3.298.
5. Lee HW, Baek LJ, Johnson KM. Isolation of Hantaan virus, the etiologic agent of Korean hemorrhagic fever, from wild urban rats. J Infect Dis. 1982;146(5):638–44. https://doi.org/10.1093/infdis/146.5.638.
6. Mertz GJ, Hjelle BL, Bryan RT. Hantavirus infection. Dis Mon. 1998;44(3):85–138. https://doi.org/10.1016/s0011-5029(98)90001-3.
7. Kuhn JH, Schmaljohn CS. A brief history of bunyaviral family hantaviridae. Diseases. 2023;11(1):38. https://doi.org/10.3390/diseases11010038. PMID: 36975587; PMCID: PMC10047430.
8. Sehgal A, Mehta S, Sahay K, Martynova E, Rizvanov A, Baranwal M, Chandy S, Khaiboullina S, Kabwe E, Davidyuk Y. Hemorrhagic fever with renal syndrome in Asia: history, pathogenesis, diagnosis, treatment, and prevention. Viruses. 2023;15(2):561. https://doi.org/10.3390/v15020561.
9. LeDuc JW, Smith GA, Pinheiro FP, Vasconcelos PF, Rosa ES, Maiztegui JI. Isolation of a Hantaan-related virus from Brazilian rats and serologic evidence of its widespread distribution in South America. Am J Trop Med Hyg. 1985;34(4):810–5. https://doi.org/10.4269/ajtmh.1985.34.810. PMID: 2862803
10. Hindrichsen S, Medeiros de Andrade A, Clement J, Leirs H, McKenna P, Matthys P, Neild GH. Hantavirus infection in Brazilian patients from Recife with suspected leptospirosis. Lancet. 1993;341(8836):50. https://doi.org/10.1016/0140-6736(93)92523-v.
11. Costa F, Porter FH, Rodrigues G, Farias H, de Faria MT, Wunder EA, Osikowicz LM, Kosoy MY, Reis MG, Ko AI, Childs JE. Infections by Leptospira interrogans, Seoul virus, and Bartonella spp. among Norway rats (Rattus norvegicus) from the urban slum environment in Brazil. Vector Borne Zoonotic Dis. 2014;14(1):33–40. https://doi.org/10.1089/vbz.2013.1378.
12. Childs JE, Ksiazek TG, Spiropoulou CF, Krebs JW, Morzunov S, Maupin GO, Gage KL, Rollin PE, Sarisky J, Enscore RE, et al. Serologic and genetic identification of Peromyscus maniculatus as the primary rodent reservoir for a new hantavirus in the southwestern United States. J Infect Dis. 1994;169(6):1271–80. https://doi.org/10.1093/infdis/169.6.1271. PMID: 8195603
13. Nichol ST, Spiropoulou CF, Morzunov S, Rollin PE, Ksiazek TG, Feldmann H, Sanchez A, Childs J, Zaki S, Peters CJ. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science. 1993;262(5135):914–7. https://doi.org/10.1126/science.8235615. PMID: 8235615
14. Llah ST, Mir S, Sharif S, Khan S, Mir MA. Hantavirus induced cardiopulmonary syndrome: a public health concern. J Med Virol. 2018;90(6):1003–9. https://doi.org/10.1002/jmv.25054. Epub 2018 Mar 15. PMID: 29446472.
15. da Silva MV, Vasconcelos MJ, Hidalgo NT, Veiga AP, Canzian M, Marotto PC, de Lima VC. Hantavirus pulmonary syndrome. Report of the first three cases in São Paulo, Brazil. Rev Inst Med Trop Sao Paulo. 1997;39(4):231–4. https://doi.org/10.1590/s0036-46651997000400010.
16. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev. 2010;23(2):412–41. https://doi.org/10.1128/CMR.00062-09. PMID: 20375360; PMCID: PMC2863364
17. Firth C, Tokarz R, Simith DB, Nunes MR, Bhat M, Rosa ES, Medeiros DB, Palacios G, Vasconcelos PF, Lipkin WI. Diversity and distribution of hantaviruses in South America. J Virol. 2012;86(24):13756–66. https://doi.org/10.1128/JVI.02341-12.
18. Willemann MC, Oliveira SV. Risk factors associated with hantavirus fatality: a regional analysis from a case-control study in Brazil. Rev Soc Bras Med Trop. 2014;47(1):47–51. https://doi.org/10.1590/0037-8682-0243-2013. PMID: 24603736
19. Seo MH, Kim CM, Kim DM, Yun NR, Park JW, Chung JK. Emerging hantavirus infection in wild rodents captured in suburbs of Gwangju Metropolitan City, South Korea. PLoS Negl Trop Dis. 2022;16(6):e0010526. https://doi.org/10.1371/journal.pntd.0010526. PMID: 35737659; PMCID: PMC9223619
20. Mills JN, Childs JE. Rodent-borne hemorrhagic fever viruses. In: Infectious diseases of wild mammals. Wiley; 2008. p. 254–69.
21. Lee HW. Hemorrhagic fever with renal syndrome in Korea. Rev Infect Dis. 1989;11(Suppl 4):S864–76. PMID: 2568676
22. Hart CA, Bennett M. Hantavirus infections: epidemiology and pathogenesis. Microbes Infect. 1999;1(14):1229–37. https://doi.org/10.1016/s1286-4579(99)00238-5. PMID: 10580279
23. Song G. Epidemiological progresses of hemorrhagic fever with renal syndrome in China. Chin Med J. 1999;112(5):472–7. PMID: 11593522
24. Zhang R, Mao Z, Yang J, Liu S, Liu Y, Qin S, Tian H, Guo S, Ren J, Shi X, Li X, Sun J, Ling F, Wang Z. The changing epidemiology of hemorrhagic fever with renal syndrome in Southeastern China during 1963–2020: a retrospective analysis of surveillance data. PLoS Negl Trop Dis. 2021;15(8):e0009673. https://doi.org/10.1371/journal.pntd.0009673. PMID: 34358248; PMCID: PMC8372920
25. Krautkrämer E, Zeier M. Old World hantaviruses: aspects of pathogenesis and clinical course of acute renal failure. Virus Res. 2014;187:59–64. https://doi.

org/10.1016/j.virusres.2013.12.043. Epub 2014 Jan 8. PMID: 24412712
26. Singh S, Numan A, Sharma D, Shukla R, Alexander A, Jain GK, Ahmad FJ, Kesharwani P. Epidemiology, virology and clinical aspects of hantavirus infections: an overview. Int J Environ Health Res. 2022;32(8):1815–26. https://doi.org/10.1080/09603123.2021.1917527. Epub 2021 Apr 22. PMID: 33886400
27. Papa A, Johnson AM, Stockton PC, Bowen MD, Spiropoulou CF, Alexiou-Daniel S, Ksiazek TG, Nichol ST, Antoniadis A. Retrospective serological and genetic study of the distribution of hantaviruses in Greece. J Med Virol. 1998;55(4):321–7. https://doi.org/10.1002/(sici)1096-9071(199808)55:4<321::aid-jmv11>3.0.co;2-h. PMID: 9661842
28. Clement J, Maes P, Lagrou K, Van Ranst M, Lameire N. A unifying hypothesis and a single name for a complex globally emerging infection: hantavirus disease. Eur J Clin Microbiol Infect Dis. 2012;31(1):1–5. https://doi.org/10.1007/s10096-011-1456-y. Epub 2011 Nov 9. PMID: 22068273; PMCID: PMC7101631
29. Lin XD, Guo WP, Wang W, Zou Y, Hao ZY, Zhou DJ, Dong X, Qu YG, Li MH, Tian HF, Wen JF, Plyusnin A, Xu J, Zhang YZ. Migration of Norway rats resulted in the worldwide distribution of Seoul hantavirus today. J Virol. 2012;86(2):972–81. https://doi.org/10.1128/JVI.00725-11. Epub 2011 Nov 16. PMID: 22090114; PMCID: PMC3255798
30. Fitte B, Brignone J, Sen C, Robles MDR. First study of Seoul virus (SEOV) in urban rodents from newly urbanized areas of Gran La Plata, Argentina. Braz J Infect Dis. 2023;27(1):102730. https://doi.org/10.1016/j.bjid.2022.102730. Epub 2022 Dec 19. PMID: 36549650; PMCID: PMC9871064
31. García PM, Percy S, Herrera AL, Donaires F, Alvarez C, Arrasco J, Cabezas C, Rodríguez H, Mamani E. Confirmación etiológica de los dos primeros casos de hantavirosis humana en el Perú [Etiologic confirmation of the first two cases of human hantavirosis in Peru]. Rev Peru Med Exp Salud Publica. 2011;28(3):566–7. https://doi.org/10.1590/s1726-46342011000300027. Spanish. PMID: 22086644
32. Knust B, Brown S, de St Maurice A, Whitmer S, Koske SE, Ervin E, Patel K, Graziano J, Morales-Betoulle ME, House J, Cannon D, Kerins J, Holzbauer S, Austin C, Gibbons-Burgener S, Colton L, Dunn J, Zufan S, Choi MJ, Davis WR, Chiang CF, Manning CR, Roesch L, Shoemaker T, Purpura L, McQuiston J, Peterson D, Radcliffe R, Garvey A, Christel E, Morgan L, Scheftel J, Kazmierczak J, Klena JD, Nichol ST, Rollin PE, Multistate Seoul Virus Outbreak Investigation Team. Seoul virus infection and spread in United States home-based Ratteries: rat and human testing results from a multistate outbreak investigation. J Infect Dis. 2020;222(8):1311–9. https://doi.org/10.1093/infdis/jiaa307. PMID: 32484879
33. Settergren B. Nephropathia epidemica (hemorrhagic fever with renal syndrome) in Scandinavia. Rev Infect Dis. 1991;13(4):736–44. https://doi.org/10.1093/clinids/13.4.736. PMID: 1681581
34. Witkowski PT, Klempa B, Ithete NL, Auste B, Mfune JK, Hoveka J, Matthee S, Preiser W, Kruger DH. Hantaviruses in Africa. Virus Res. 2014;187:34–42. https://doi.org/10.1016/j.virusres.2013.12.039. Epub 2014 Jan 7. PMID: 24406800
35. Castel G, Filippone C, Tatard C, Vigan J, Dobigny G. Role of seaports and imported rats in Seoul hantavirus circulation, Africa. Emerg Infect Dis. 2023;29(1):20–5. https://doi.org/10.3201/eid2901.221092. PMID: 36573519; PMCID: PMC9796207
36. Martinez VP, Bellomo C, San Juan J, Pinna D, Forlenza R, Elder M, Padula PJ. Person-to-person transmission of Andes virus. Emerg Infect Dis. 2005;11(12):1848–53. https://doi.org/10.3201/eid1112.050501. PMID: 16485469; PMCID: PMC3367635
37. Jiang H, Du H, Wang LM, Wang PZ, Bai XF. Hemorrhagic fever with renal syndrome: pathogenesis and clinical picture. Front Cell Infect Microbiol. 2016;6:1. https://doi.org/10.3389/fcimb.2016.00001.
38. Korva M, Saksida A, Kunilo S, Vidan Jeras B, Avsic-Zupanc T. HLA-associated hemorrhagic fever with renal syndrome disease progression in slovenian patients. Clin Vaccine Immunol. 2011;18(9):1435–40. https://doi.org/10.1128/CVI.05187-11. Epub 2011 Jul 20. PMID: 21775516; PMCID: PMC3165220
39. Wu G, Xia Z, Wang F, Wu J, Cheng D, Chen X, Liu H, Du Z. Investigation on risk factors of haemorrhagic fever with renal syndrome (HFRS) in Xuancheng City in Anhui Province, Mainland China. Epidemiol Infect. 2020;148:e248. https://doi.org/10.1017/S0950268820002344. PMID: 33004084; PMCID: PMC7592102
40. Childs JE, Mills JN, Glass GE. Rodent-borne hemorrhagic fever viruses: a special risk for mammalogists? J Mammal. 1995;6:664–80.
41. Milholland MT, Castro-Arellano I, Garcia-Peña GE, Mills JN. The ecology and phylogeny of hosts drive the enzootic infection cycles of hantaviruses. Viruses. 2019;11(7):671. https://doi.org/10.3390/v11070671. PMID: 31340455; PMCID: PMC6669546
42. Ashique S, Sandhu NK, Das S, Haque SN, Koley K. Global comprehensive outlook of hantavirus contagion on humans: a review. Infect Disord Drug Targets. 2022;22(3):e050122199975. https://doi.org/10.2174/1871526522666220105110819. PMID: 34986775
43. Campos GM, Moro de Sousa RL, Badra SJ, Pane C, Gomes UA, Figueiredo LT. Serological survey of hantavirus in Jardinopolis County, Brazil. J Med Virol. 2003;71(3):417–22. https://doi.org/10.1002/jmv.10489. PMID: 12966548

44. Vial PA, Ferrés M, Vial C, Klingström J, Ahlm C, López R, Le Corre N, Mertz GJ. Hantavirus in humans: a review of clinical aspects and management. Lancet Infect Dis. 2023;23(9):e371–82. https://doi.org/10.1016/S1473-3099(23)00128-7. Epub 2023 Apr 24. PMID: 37105214
45. Koehler FC, Di Cristanziano V, Späth MR, Hoyer-Allo KJR, Wanken M, Müller RU, Burst V. The kidney in hantavirus infection-epidemiology, virology, pathophysiology, clinical presentation, diagnosis and management. Clin Kidney J. 2022;15(7):1231–52. https://doi.org/10.1093/ckj/sfac008.
46. Noh JY, Jung J, Song JW. Hemorrhagic fever with renal syndrome. Infect Chemother. 2019;51(4):405–13. https://doi.org/10.3947/ic.2019.51.4.405. Epub 2019 Oct 31. Erratum in: Infect Chemother. 2020 Jun;52(2):305–306. PMID: 31668027; PMCID: PMC6940369
47. Vapalahti O, Mustonen J, Lundkvist A, Henttonen H, Plyusnin A, Vaheri A. Hantavirus infections in Europe. Lancet Infect Dis. 2003;3(10):653–61. https://doi.org/10.1016/s1473-3099(03)00774-6. PMID: 14522264
48. Mustonen J, Mäkelä S, Outinen T, Laine O, Jylhävä J, Arstila PT, Hurme M, Vaheri A. The pathogenesis of nephropathia epidemica: new knowledge and unanswered questions. Antivir Res. 2013;100(3):589–604. https://doi.org/10.1016/j.antiviral.2013.10.001. Epub 2013 Oct 12. PMID: 24126075
49. Clement J, Kuypers D, Meijers B, Van Ranst M. Hantavirus infection with renal involvement do not result in chronic renal diseases or end-stage renal failure. J Nephrol Renal Dis. 2017;1:1.
50. Engler O, Klingstrom J, Aliyev E, Niederhauser C, Fontana S, Strasser M, Portmann J, Signer J, Bankoul S, Frey F, Hatz C, Stutz A, Tschaggelar A, Mutsch M. Seroprevalence of hantavirus infections in Switzerland in 2009: difficulties in determining prevalence in a country with low endemicity. Euro Surveill. 2013;18(50):20660. https://doi.org/10.2807/1560-7917.es2013.18.50.20660. PMID: 24342520
51. Mattar S, Guzmán C, Figueiredo LT. Diagnosis of hantavirus infection in humans. Expert Rev Anti-Infect Ther. 2015;13(8):939–46. https://doi.org/10.1586/14787210.2015.1047825. Epub 2015 Jun 19. PMID: 26091780
52. Figueiredo LT, Moreli ML, Borges AA, et al. Diagnosis of hantavirus relies on demonstration of immune response, which becomes evident within 2 to 8 days of acute onset. Braz J Med Biol Res. 2008;41:596–9.
53. Figueiredo LT, Moreli ML, Borges AA, de Figueiredo GG, Badra SJ, Bisordi I, Suzuki A, Capria S, Padula P. Evaluation of an enzyme-linked immunosorbent assay based on Araraquara virus recombinant nucleocapsid protein. Am J Trop Med Hyg. 2009;81(2):273–6. PMID: 19635882
54. Padula PJ, Rossi CM, Valle MOD, Martínez PV, Colavecchia SB, Edelstein A, Miguel SDL, Rabinovich RD, Segura EL. Development and evaluation of a solid-phase enzyme immunoassay based on Andes hantavirus recombinant nucleoprotein. J Med Microbiol. 2000;49(2):149–55. https://doi.org/10.1099/0022-1317-49-2-149. PMID: 10670565
55. Amada T, Yoshimatsu K, Koma T, Shimizu K, Gamage CD, Shiokawa K, Nishio S, Ahlm C, Arikawa J. Development of an immunochromatography strip test based on truncated nucleocapsid antigens of three representative hantaviruses. Virol J. 2014;11:87. https://doi.org/10.1186/1743-422X-11-87. PMID: 24885901; PMCID: PMC4047433
56. Hujakka H, Koistinen V, Kuronen I, Eerikäinen P, Parviainen M, Lundkvist A, Vaheri A, Vapalahti O, Närvänen A. Diagnostic rapid tests for acute hantavirus infections: specific tests for Hantaan, Dobrava and Puumala viruses versus a hantavirus combination test. J Virol Methods. 2003;108(1):117–22. https://doi.org/10.1016/s0166-0934(02)00282-3. PMID: 12565162
57. Yoshimatsu K, Arikawa J. Serological diagnosis with recombinant N antigen for hantavirus infection. Virus Res. 2014;187:77–83. https://doi.org/10.1016/j.virusres.2013.12.040. Epub 2014 Jan 31. PMID: 24487183
58. Evander M, Eriksson I, Pettersson L, Juto P, Ahlm C, Olsson GE, Bucht G, Allard A. Puumala hantavirus viremia diagnosed by real-time reverse transcriptase PCR using samples from patients with hemorrhagic fever and renal syndrome. J Clin Microbiol. 2007;45(8):2491–7. https://doi.org/10.1128/JCM.01902-06. Epub 2007 May 30. PMID: 17537944; PMCID: PMC1951205
59. Lagerqvist N, Hagström Å, Lundahl M, Nilsson E, Juremalm M, Larsson I, Alm E, Bucht G, Ahlm C, Klingström J. Molecular diagnosis of hemorrhagic fever with renal syndrome caused by Puumala virus. J Clin Microbiol. 2016;54(5):1335–9. https://doi.org/10.1128/JCM.00113-16. Epub 2016 Mar 9. PMID: 26962084; PMCID: PMC4844727
60. Nunes BTD, de Mendonça MHR, Simith DB, Moraes AF, Cardoso CC, Prazeres ITE, de Aquino AA, Santos ADCM, Queiroz ALN, Rodrigues DSG, Andriolo RB, Travassos da Rosa ES, Martins LC, Vasconcelos PFDC, Medeiros DBA. Development of RT-qPCR and semi-nested RT-PCR assays for molecular diagnosis of hantavirus pulmonary syndrome. PLoS Negl Trop Dis. 2019;13(12):e0007884. https://doi.org/10.1371/journal.pntd.0007884. PMID: 31877142; PMCID: PMC6932758
61. Vial C, Martinez-Valdebenito C, Rios S, Martinez J, Vial PA, Ferres M, Rivera JC, Perez R, Valdivieso F. Molecular method for the detection of Andes hantavirus infection: validation for clinical diagnostics. Diagn Microbiol Infect Dis. 2016;84(1):36–9. https://doi.org/10.1016/j.diagmicrobio.2015.07.019. Epub 2015 Jul 29. PMID: 26508102; PMCID: PMC4754785

62. Zhang L, Ma QS, Zhang Y, Sun BC, Zhao LY. Analysis of misdiagnosed cases of hemorrhagic fever with renal syndrome in children: two cases and literature review. BMC Nephrol. 2019;20(1):383. https://doi.org/10.1186/s12882-019-1562-0. PMID: 31646967; PMCID: PMC6813044
63. Chand S, Thapa S, Kon S, Johnson SC, Poeschla EM, Franco-Paredes C, Rodríguez-Morales AJ, Mattar S, Henao-Martínez AF. Hantavirus infection with renal failure and proteinuria, Colorado, USA, 2019. Emerg Infect Dis. 2020;26(2):383–5. https://doi.org/10.3201/eid2602.191349. PMID: 31961310; PMCID: PMC6986832
64. Ren D, Fu S, Yan T, Ni T, Zhang Z, Zhang M, Zhou J, Yang N, Yang Y, He Y, Chen T, Zhao Y, Liu J. The clinical characteristics and outcomes of hemorrhagic fever with renal syndrome in pregnancy. Front Med (Lausanne). 2022;9:839224. https://doi.org/10.3389/fmed.2022.839224. PMID: 35265645; PMCID: PMC8899103
65. Ferreira MS. Hantaviroses. Rev Soc Bras Med Trop. 2003;36(1):81–96. Portuguese. Epub 2003 Apr 22. PMID: 12715067
66. Noack D, Goeijenbier M, Reusken CBEM, Koopmans MPG, Rockx BHG. Orthohantavirus pathogenesis and cell tropism. Front Cell Infect Microbiol. 2020;10:399. https://doi.org/10.3389/fcimb.2020.00399. PMID: 32903721; PMCID: PMC7438779
67. Avšič-Županc T, Saksida A, Korva M. Hantavirus infections. Clin Microbiol Infect. 2019;21S:e6–e16. https://doi.org/10.1111/1469-0691.12291. Epub 2015 Jun 22. PMID: 24750436
68. Kyriakidis I, Papa A. Serum TNF-α, sTNFR1, IL-6, IL-8 and IL-10 levels in hemorrhagic fever with renal syndrome. Virus Res. 2013;175(1):91–4. https://doi.org/10.1016/j.virusres.2013.03.020. Epub 2013 Apr 17. PMID: 23603136
69. Rista E, Pilaca A, Akshija I, Rama A, Harja E, Puca E, Bino S, Cadri V, Kota M, Nestor T, Arjan H. Hemorrhagic fever with renal syndrome in Albania. Focus on predictors of acute kidney injury in HFRS. J Clin Virol. 2017;91:25–30. https://doi.org/10.1016/j.jcv.2017.03.021. Epub 2017 Mar 31. PMID: 28411480
70. Garanina E, Martynova E, Davidyuk Y, Kabwe E, Ivanov K, Titova A, Markelova M, Zhuravleva M, Cherepnev G, Shakirova VG, Khaertynova I, Tarlinton R, Rizvanov A, Khaiboullina S, Morzunov S. Cytokine storm combined with humoral immune response defect in fatal hemorrhagic fever with renal syndrome case, Tatarstan, Russia. Viruses. 2019;11(7):601. https://doi.org/10.3390/v11070601. PMID: 31269734; PMCID: PMC6669480
71. Mustonen J, Outinen T, Laine O, Pörsti I, Vaheri A, Mäkelä S. Kidney disease in Puumala hantavirus infection. Infect Dis (Lond). 2017;49(5):321–32. https://doi.org/10.1080/23744235.2016.1274421. Epub 2017 Jan 3. PMID: 28049381
72. Nolte KB, Feddersen RM, Foucar K, Zaki SR, Koster FT, Madar D, Merlin TL, McFeeley PJ, Umland ET, Zumwalt RE. Hantavirus pulmonary syndrome in the United States: a pathological description of a disease caused by a new agent. Hum Pathol. 1995;26(1):110–20. https://doi.org/10.1016/0046-8177(95)90123-x. PMID: 7821907
73. Zaki SR, Greer PW, Coffield LM, Goldsmith CS, Nolte KB, Foucar K, Feddersen RM, Zumwalt RE, Miller GL, Khan AS, et al. Hantavirus pulmonary syndrome. Pathogenesis of an emerging infectious disease. Am J Pathol. 1995;146(3):552–79. PMID: 7887439; PMCID: PMC1869168
74. Mir S. Hantavirus induced kidney disease. Front Med (Lausanne). 2022;8:795340. https://doi.org/10.3389/fmed.2021.795340. PMID: 35118091; PMCID: PMC8804099
75. Gnemmi V, Verine J, Vrigneaud L, Glowacki F, Ratsimbazafy A, Copin MC, Dewilde A, Buob D. Microvascular inflammation and acute tubular necrosis are major histologic features of hantavirus nephropathy. Hum Pathol. 2015;46(6):827–35. https://doi.org/10.1016/j.humpath.2015.02.002. Epub 2015 Feb 19. PMID: 25791582
76. Afzal S, Ali L, Batool A, Afzal M, Kanwal N, Hassan M, Safdar M, Ahmad A, Yang J. Hantavirus: an overview and advancements in therapeutic approaches for infection. Front Microbiol. 2023;14:1233433. https://doi.org/10.3389/fmicb.2023.1233433. Erratum in: Front Microbiol. 2023 Dec 12;14:1343080. PMID: 37901807; PMCID: PMC10601933
77. Dheerasekara K, Sumathipala S, Muthugala R. Hantavirus infections-treatment and prevention. Curr Treat Options Infect Dis. 2020;12(4):410–21. https://doi.org/10.1007/s40506-020-00236-3. Epub 2020 Oct 29. PMID: 33144850; PMCID: PMC7594967
78. Brocato RL, Hooper JW. Progress on the prevention and treatment of hantavirus disease. Viruses. 2019;11(7):610. https://doi.org/10.3390/v11070610. PMID: 31277410; PMCID: PMC6669544
79. Huggins JW, Kim GR, Brand OM, McKee KT Jr. Ribavirin therapy for Hantaan virus infection in suckling mice. J Infect Dis. 1986;153(3):489–97. https://doi.org/10.1093/infdis/153.3.489. PMID: 2869089
80. Malinin OV, Platonov AE. Insufficient efficacy and safety of intravenous ribavirin in treatment of haemorrhagic fever with renal syndrome caused by Puumala virus. Infect Dis (Lond). 2017;49(7):514–20. https://doi.org/10.1080/23744235.2017.1293841. Epub 2017 Mar 3. PMID: 28276794
81. Safronetz D, Falzarano D, Scott DP, Furuta Y, Feldmann H, Gowen BB. Antiviral efficacy of favipiravir against two prominent etiological agents of hantavirus pulmonary syndrome. Antimicrob Agents Chemother. 2013;57(10):4673–80. https://doi.org/10.1128/AAC.00886-13. Epub 2013 Jul 15. PMID: 23856782; PMCID: PMC3811478

82. Murphy ME, Kariwa H, Mizutani T, Yoshimatsu K, Arikawa J, Takashima I. In vitro antiviral activity of lactoferrin and ribavirin upon hantavirus. Arch Virol. 2000;145(8):1571–82. https://doi.org/10.1007/s007050070077. PMID: 11003470
83. Bird BH, Shrivastava-Ranjan P, Dodd KA, Erickson BR, Spiropoulou CF. Effect of Vandetanib on Andes virus survival in the hamster model of Hantavirus pulmonary syndrome. Antivir Res. 2016;132:66–9. https://doi.org/10.1016/j.antiviral.2016.05.014. Epub 2016 May 24. PMID: 27233645
84. Vial PA, Valdivieso F, Calvo M, Rioseco ML, Riquelme R, Araneda A, Tomicic V, Graf J, Paredes L, Florenzano M, Bidart T, Cuiza A, Marco C, Hjelle B, Ye C, Hanfelt-Goade D, Vial C, Rivera JC, Delgado I, Mertz GJ, Hantavirus Study Group in Chile. A non-randomized multicentre trial of human immune plasma for treatment of hantavirus cardiopulmonary syndrome caused by Andes virus. Antivir Ther. 2015;20(4):377–86. https://doi.org/10.3851/IMP2875. Epub 2014 Oct 15. PMID: 25316807
85. Seto WH. Airborne transmission and precautions: facts and myths. J Hosp Infect. 2015;89(4):225–8. https://doi.org/10.1016/j.jhin.2014.11.005. Epub 2014 Dec 13. PMID: 25578684; PMCID: PMC7132528
86. Li Z, Zeng H, Wang Y, Zhang Y, Cheng L, Zhang F, Lei Y, Jin B, Ma Y, Chen L. The assessment of Hantaan virus-specific antibody responses after the immunization program for hemorrhagic fever with renal syndrome in Northwest China. Hum Vaccin Immunother. 2017;13(4):802–7. https://doi.org/10.1080/21645515.2016.1253645. Epub 2016 Nov 8. PMID: 27824286; PMCID: PMC5404621
87. Song JY, Woo HJ, Cheong HJ, Noh JY, Baek LJ, Kim WJ. Long-term immunogenicity and safety of inactivated Hantaan virus vaccine (Hantavax™) in healthy adults. Vaccine. 2016;34(10):1289–95. https://doi.org/10.1016/j.vaccine.2016.01.031. Epub 2016 Jan 28. PMID: 26826547
88. Mohsen MO, Zha L, Cabral-Miranda G, Bachmann MF. Major findings and recent advances in virus-like particle (VLP)-based vaccines. Semin Immunol. 2017;34:123–32. https://doi.org/10.1016/j.smim.2017.08.014. Epub 2017 Sep 5. PMID: 28887001
89. Jiang DB, Sun LJ, Cheng LF, Zhang JP, Xiao SB, Sun YJ, Yang SY, Wang J, Zhang FL, Yang K. Recombinant DNA vaccine of hantavirus Gn and LAMP1 induced long-term immune protection in mice. Antivir Res. 2017;138:32–9. https://doi.org/10.1016/j.antiviral.2016.12.001. Epub 2016 Dec 5. PMID: 27923570
90. Kamrud KI, Hooper JW, Elgh F, Schmaljohn CS. Comparison of the protective efficacy of naked DNA, DNA-based Sindbis replicon, and packaged Sindbis replicon vectors expressing Hantavirus structural genes in hamsters. Virology. 1999;263(1):209–19. https://doi.org/10.1006/viro.1999.9961. PMID: 10544095
91. Hooper JW, Custer DM, Thompson E, Schmaljohn CS. DNA vaccination with the Hantaan virus M gene protects Hamsters against three of four HFRS hantaviruses and elicits a high-titer neutralizing antibody response in Rhesus monkeys. J Virol. 2001;75(18):8469–77. https://doi.org/10.1128/jvi.75.18.8469-8477.2001. PMID: 11507192; PMCID: PMC115092
92. Hooper JW, Moon JE, Paolino KM, Newcomer R, McLain DE, Josleyn M, Hannaman D, Schmaljohn C. A Phase 1 clinical trial of Hantaan virus and Puumala virus M-segment DNA vaccines for haemorrhagic fever with renal syndrome delivered by intramuscular electroporation. Clin Microbiol Infect. 2014;20(Suppl 5):110–7. https://doi.org/10.1111/1469-0691.12553. Epub 2014 Mar 7. PMID: 24447183
93. Ministério da Saúde. Secretaria de Vigilância em Saúde e Ambiente. Departamento de Articulação Estratégica de Vigilância em Saúde e Ambiente. Guia de vigilância em saúde. Hantavirose. [recurso eletrônico] 5. ed. rev. e atual. Brasília: Ministério da Saúde.1.126 p; 2022.
94. Oliveira SV, Folster I, Zeccer S, et al. Investigação de ratada associada a florescimento e frutificação de taquaras em São Francisco do Sul, Santa Catarina, Brasil, 2012. Revista Baiana de Saúde Pública. 2014;37:1071.
95. Iversson LB, Travassos da Rosa APA, Rosa MDB, et al. Infecção humana por hantavírus no sul e sudeste do Brasil. Revista de Assistência Médica Brasileira. 1994;40:85–92.
96. Clement J, Neild G, Hinrichsen SL, et al. Urban leptospirosis versus urban hantavírus infection in Brazil. Lancet. 1999;354:2003–4.
97. Pereira LE, Souza LTM, Souza RP, et al. Histórico da Vigilância Ecoepidemiológica do Hantavírus no Brasil. Revista CIP. 1999;3:5–12.
98. Badra SJ, Maia FGM, Figueiredo GG, et al. A retrospective serologic survey of hantavirus infections in the county of Cássia dos Coqueiros, state of São Paulo, Brazil. Rev Soc Bras Med Trop. 2012;45:468–70.

17 HIV and Kidney Disease

Geraldo Bezerra da Silva Junior,
Juliana Gomes Ramalho de Oliveira,
Elizabeth De Francesco Daher,
and Saraladevi Naicker

17.1 Introduction

Approximately 39.9 million people worldwide were living with the human immunodeficiency virus (HIV) in 2023, with 1.3 million new infections; 25 million live in Africa; 30.7 million were accessing antiretroviral therapy, and 42.3 million people have died from AIDS-related illnesses since the start of the epidemic [1]. Due to an increase in access to antiretroviral treatment (ART) and consequently improvement in the health condition of people living with HIV, the spectrum of HIV-associated kidney disease has changed [2].

HIV is considered a public health threat, and a priority included in the agenda of the Sustainable Development Goals. Since the beginning of the AIDS epidemic in the 1980s, there are the lowest rates of AIDS-related deaths and the highest number of people receiving ART in the world [3].

In the last two decades, with the advent of antiretroviral therapy (ART) and the increase in life expectancy of individuals infected with HIV, this infection has become a chronic disease [4]. Therefore, emerging challenges are the conditions associated with inflammation, aging, cardiovascular disease, cancer, diabetes, liver disease, and bone and kidney disease of several etiologies [5]. Diabetes mellitus and systemic arterial hypertension are the main risk factors for kidney disease in the general population, increasing the risk of chronic kidney disease (CKD) by tenfold, and they are becoming increasingly common in people living with HIV [6].

HIV infection is an important risk factor for kidney disease, both in its acute and chronic forms, and prolonged exposure to ART may cause or exacerbate kidney injury [7]. Investigation of acute kidney injury (AKI) in people living with HIV (PLWH) is similar to that recommended for other patients, and the most frequent causes of kidney injury in outpatients with HIV are drug toxicity and dehydration that occur with prerenal AKI [8]. Hospitalized HIV patients with sepsis or those taking nephrotoxic drugs are at increased risk for acute tubular necrosis and acute interstitial nephritis [4].

With the World Health Organization recommendation for the start of ART in all patients with HIV infection, regardless of CD4 cell count or

G. Bezerra da Silva Junior (✉) · J. G. R. de Oliveira
Post-Graduation Programs in Public Health and Medical Sciences, School of Medicine, University of Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

E. De Francesco Daher
Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

S. Naicker
Department of Internal Medicine, School of Clinical Medicine, University of the Witwatersrand, Johannesburg, Gauteng, South Africa
e-mail: saraladevi.naicker@wits.ac.za

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_17

disease stage [9], early detection and appropriate treatment of kidney disease are critical to achieve a better prognosis [10]. Due to partial or complete kidney excretion of many antiretrovirals, the doses need to be adjusted in patients with CKD, according to glomerular filtration rate (GFR) [7, 11].

In the initial laboratory assessment of PLWH, kidney function should be assessed through creatinine measurement and estimated GFR (eGFR) and urinalysis according to international guidelines [7, 12]. As for the clinical follow-up, prior to the start of ART, creatinine and eGFR analysis should be repeated annually, except for those with specific conditions, such as the use of tenofovir or other nephrotoxic drugs, or with eGFR <60 mL/min or increased risk for kidney disease, such as individuals with diabetes and hypertension, in whom follow-up should be performed at intervals of 3–6 months [13].

Before the availability of ART, the most common kidney disease observed in PLWH was "HIVAN" (HIV-associated nephropathy), an injury directly associated with the virus [2]. Currently, the spectrum of kidney diseases associated with HIV is a combination of comorbidities and toxicities of drugs in a population living longer with a chronic viral disease [2]. Table 17.1

Table 17.1 Spectrum of HIV-associated kidney diseases—data from large studies based on kidney biopsies from South Africa and the USA

Study details and biopsy findings			South Africa Johannesburg (2022)[a]	Cape Town (2023)[b]	USA New York (2020)[c]
N			690	671	437
Kidney histology (%)					
Glomerular dominant	Total		76.2	63.5	44
	Podocytopathies	Total	44.5	46.5	27
		Classic HIVAN	25.8	43.7	14
		FSGS (NOS)	13.9	2.1	12
		Other podocytopathy in the setting of HIV	4.8	0.7	2
	Immune complex-mediated glomerular disease	Total	31.7	17	17
		Uncharacterized ICGN with no other etiology than HIV	11.2	NR	2
		Membranous nephropathy in the setting of HIV	6.5	2.2	3
		Membranoproliferative glomerulonephritis in the setting of HIV	6.4	5.2	NR
		IgA nephropathy in the setting of HIV	0.7	0.5	5
		Other	6.9	9.1	5
Tubulointerstitial dominant		Total	10.5	24.7	26
		Tubulointerstitial nephritis	7	16	3
		Acute tubular injury	3	3.1	8
		Tenofovir nephrotoxicity	NR	3.6	13
		Other	0.5	2.0	2.0
Vascular dominant		Total	1.4	0.3	2
Other		Total	11.9	11.6	28
		Hypertensive nephrosclerosis	6.2	4.0	NR
		Diabetic kidney disease	3.6	4.0	16
		Other	2.1	3.6	12

Adapted from Diana & Naicker [2]
[a]Diana et al. [14]
[b]Wearne et al. [15]
[c]Kudose et al. [16]

summarizes the spectrum of kidney histology of three large studies in PLWH in South Africa and the USA.

17.2 Acute Kidney Injury in HIV

Acute kidney injury (AKI) can be defined, according to the Kidney Improving Global Outcomes (KDIGO) guidelines, as one of the following criteria: increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h; or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 h [17].

According to Wyatt and Klotman [18], the incidence of AKI in PLWH is higher than in uninfected patients. It is also noted that the incidence of AKI in HIV patients has increased over time, as demonstrated by a study of hospitalized adults in the state of New York, USA, where data from 1995 (prior to the introduction of the highly active antiretroviral therapy—HAART) as well as data from 2003 (after the introduction of HAART) were analyzed. Compared with uninfected hospitalized patients, AKI was identified in a significantly higher proportion of hospitalized and HIV-infected patients, both in 1995 (2.9 vs. 1%) and in 2003 (6 vs. 2.7%). Among HIV-infected patients, a twofold higher proportion was identified with AKI in 2003, although in-hospital mortality was lower [19].

The most common causes of AKI in the clinical setting of HIV infection include drug toxicity, especially ART, volume depletion, sepsis, and liver disease. The risk factors are similar to those in the general population and include older age, high blood pressure, diabetes mellitus, preexisting CKD, family history of kidney disease, advanced HIV disease, hepatitis C virus (HCV) coinfection [20], severe systemic disease or infection, exposure to nephrotoxic agents, and low CD4 count [21].

The high prevalence of AKI in PLWH has been verified in several studies [22, 23]. In a study of 754 PLWH undergoing outpatient follow-up, the incidence of AKI was 5.9 cases per 100 patient-years, with at least one episode in almost 10% of patients [22]. Intrinsic renal causes were the most common factors of AKI (46%), and most cases were attributed to acute ischemic tubular necrosis or nephrotoxic drugs and, to a lesser extent, radiocontrast nephropathy (Table 17.2). In the same study, prerenal AKI was frequent (38%) and was associated with volume depletion, sepsis, and liver disease. Obstructive (calculi, crystalluria, and macroscopic hematuria) and unknown causes comprised the remaining cases [22]. Most infections detected in this group of patients were AIDS-defining infections, showing that even among outpatients in the post-ART era, opportunistic infections are still common causes of AKI. Medications were associated with a third of the events, causing acute tubular necrosis, acute interstitial nephritis, or obstruction due to crystalluria. Antibiotic and antiretroviral agents were the most common nephrotoxic drugs, with amphotericin B and indinavir being the most commonly implicated agents [22, 24].

The differential diagnoses of AKI in PLWH are extensive and include virus-related conditions, such as HIVAN and drug-related kidney injury, and causes unrelated to HIV. AKI is highly prevalent and is associated with increased morbidity and mortality. In the USA, the analysis of 12 million hospital discharges showed that mortality during hospitalization was nearly sixfold higher among PLWH with documented AKI [21].

Table 17.2 Causes of acute kidney injury in HIV-infected patients

Prerenal AKI
Hypovolemia: diarrhea, nausea, vomiting, decreased oral intake, hypotension, sepsis, liver disease, hypoalbuminemia (nephrotic syndrome, proteinuria, malnutrition)
Intrinsic kidney injury
Acute tubular necrosis
Ischemia: hypovolemia, shock, sepsis, cardiopulmonary impairment
Nephrotoxicity: medications, radiocontrast agents
Rhabdomyolysis
Parenchymal infection (mycobacteria, fungus, virus)
Interstitial nephritis
Hemolytic uremic syndrome
Glomerular disease: HIV-associated nephropathy, glomerulonephritis

In Brazil, researchers have identified septic shock and the need for mechanical ventilation as independent risk factors for mortality in patients with HIV and AKI admitted to an intensive care unit [23].

Antiretroviral therapy became available for a higher number of people worldwide, and it impacted on the pattern of HIV-associated kidney diseases. There is currently an association between comorbidities seen in ageing people with HIV, nephrotoxicity related to HIV treatment, and all other associated diseases that injures the kidneys due to HIV infection and its related complications [2].

17.3 HIV-Associated Nephropathies

HIVAN was originally described in 1984 as a focal and segmental glomerulosclerosis (FSGS) with a clinical presentation that included nephrotic proteinuria and rapid renal function decline. Some authors believe that the prevalence of kidney disease seems to increase in the HIV-infected population [21]. Prior to the implementation of ART, HIVAN progressed rapidly to the terminal stages of CKD, but the continued use of these drugs reduced the risk of nephropathy by 60% [11].

When identifying kidney disease at the initial diagnosis of HIV infection, careful assessment of risk factors and screening for kidney disease are recommended. HIVAN needs to be diagnosed early because, if left untreated, it is associated with a worse prognosis [25]. The main risk factors to be evaluated include high blood pressure, diabetes, hepatitis C, potentially nephrotoxic drugs, family history of kidney disease, black ethnicity, advanced HIV disease, cardiovascular disease, smoking, and cocaine exposure. Cocaine, a well-described nephrotoxin, frequently used by PLWH, has been associated with alterations in renal hypertension in patients with HIV [25].

Similar to the natural history of CKD, HIVAN occurs more frequently in black patients [8] and has been described in 3.5–10% of individuals with HIV in the USA, predominantly among those of African descent [11]. The disease trajectory is considerably more aggressive in black PLWH than in whites. Among the 4259 patients observed at the Johns Hopkins HIV Cohort Clinic from 1990 to 2004, the risk of CKD was twofold higher among blacks [21].

HIVAN is characterized as a collapsing focal segmental glomerulosclerosis (FSGS) occurring predominantly in African descent people [29]. According to Wyatt and Klotman [26], the strong association between the predilection for HIVAN in people of black ethnicity indicates that host genetic factors are important. Human genetic studies have identified single-nucleotide polymorphisms in the apolipoprotein L1 gene (*APOL1*) on chromosome 22, which are strongly linked to the increased risk of HIVAN, as well as idiopathic FSGS. There are two variants in the *APOL1* (G1 and G2) associated with advanced CKD in HIVAN. HIV is one of the triggers of kidney disease in people with *APOL1* variants [27]. People in Nigeria with *APOL1* gene have a 2 times higher risk of FSGS and HIVAN [28]. This genotype has also been linked to proteinuria not associated with FSGS in people with HIV, and the mechanism linking genetics and kidney injury remains to be elucidated [29].

Morphologically, HIVAN is a variant of FSGS characterized by the collapse of glomerular tufts. The unique feature of HIVAN, however, is the marked hypertrophy of glomerular epithelial cells that leads to hyperplasia, mimicking epithelial crescents—"pseudo-crescents." Immunohistochemical studies demonstrated an increased expression of podocyte proliferation markers, and tubulo-reticular-endothelial inclusions (related to high interferon γ plasma levels) were detected through electron microscopy [30]. Podocytes are highly differentiated and quiescent cells in the normal glomerulus. In HIVAN, they show phenotype deregulation, characterized by increased proliferation, apoptosis, and de-differentiation [30]. Viruses can act on podocytes by direct infection or by the release of inflammatory cytokines that interact with their receptors [31].

Clinically, HIVAN presents with progressive azotemia, significant proteinuria, and little or no

peripheral edema in patients with advanced HIV disease. Proteinuria is a defining characteristic of FSGS, typically accompanied by hypoalbuminemia, hypercholesterolemia, and peripheral edema. Despite the common finding of gross proteinuria and hypoalbuminemia, the absence of clinical signs leads to the late diagnosis of this glomerulopathy [32].

The most effective treatment for HIVAN is the use of ART and infection control, as well as the prescription of antiproteinuric drugs, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) [13].

Several other glomerulopathies may occur in PLWH, such as HIV-related immune-complex mediated kidney disease, IgA nephropathy, lupus-like glomerulonephritis, postinfectious glomerulonephritis, and HCV-associated membranoproliferative glomerulonephritis. Moreover, thrombotic microangiopathy and traditional forms of glomerular impairment, such as those related to diabetes and hypertension, may also occur [8]. HIV-associated thrombotic microangiopathy may present with severe AKI and result in CKD in some patients, due to incomplete recovery from the acute injury [33]. However, it is considered a rare complication in the HAART era [34].

According to Cohen et al., HIV-associated nephropathy can now be described as "caused by complex interactions between the virus (renal cell infection and the effect of viral proteins), host genotype, host response (interferon production) and, probably the most important, effective treatment" [4].

Specific treatment with APOL1 small molecule inhibitors, APOL1 antisense oligonucleotides, and APOL1-associated inflammatory pathway inhibitors are all currently investigated as potentially effective for HIVAN [27, 35].

17.4 Immune Complex-Associated Kidney Disease

In contrast to HIVAN, HIV-specific immune complex-mediated glomerulonephritis has no strong racial predilection, and its incidence increased after the introduction of ART [13]. Histological patterns can be separated into four categories:

- Immune complex-mediated glomerulonephritis
- IgA nephropathy
- Inflammatory disease
- Lupus-like disease

Immune complexes with HIV antigens have been identified in the circulation and renal tissue of HIV-infected patients with IgA nephritis and immune complex glomerulonephritis. As with HIVAN, a kidney biopsy is required for a definitive diagnosis. Antiretroviral therapy reduces the amount of circulating viral antigens and the formation of immune complexes [25].

IgA nephropathy is not common in the context of HIV infection, and reports in the literature indicate that kidney disease followed a benign course similar to that observed in the absence of the virus [18]. However, there is also evidence of a more aggressive course of disease, similar to lupus glomerulonephritis, in which patients progressed to end-stage kidney failure within 1 year. Unlike other HIV-associated immune complex diseases, lupus-like kidney disease may be associated with black ethnicity [18]. With improved survival, the number of patients living with end-stage kidney disease attributed to HIVAN continues to increase [26].

17.5 HIV-Associated Chronic Kidney Disease

CKD is a public health problem that affects approximately 10% of the world's population [36]. In Brazil, it is estimated that in 2022, the prevalence of positive-HIV serology in patients undergoing dialysis treatment was 1.1% [37]. According to the Ministry of Health's therapeutic guidelines, the specific risk factors for developing CKD in PLWH are black ethnicity, presence of proteinuria, family history of nephropathy, high viral load, low CD4+ T lymphocyte count, diagnosis of diabetes and hypertension, older

age, smoking, and obesity [13]. The burden of CKD on PLWH is heavy worldwide, especially in African patients [38]. The "Kidney Disease: Improving Global Outcomes" (KDIGO), at a conference that brought together nephrology and other specialists, established clinical guidelines for the prevention and treatment of kidney disease in individuals with HIV [7].

A meta-analysis of articles on the prevalence of CKD in HIV-positive adults showed that there is no consensus among researchers about the best equation for estimating GFR, and thus, the most commonly used is Chronic Kidney Disease Epidemiology (CKD-EPI), which is the most recommended in general [38–40].

In a study that included more than 16,500 HIV-positive participants treated at 103 centers, data from 6843 participants who had at least three serum creatinine measurements were analyzed. They were followed for an average of 4 years, accumulating a total of 21,482 person-years. In this study, CKD was defined as eGFR estimated at 60 mL/min or less, persistently, if the baseline level was above 60 mL/ min, or a 25% reduction if the baseline was less than 60 mL/min, when using the Cockcroft-Gault formula. A total of 225 study participants (3.3%) developed CKD during follow-up, with an incidence rate of 1.1 per 100 person-years. The rate increased over time from less than 0.5% after the first year to 1.5% after the second year, to approximately 4.5% after 4 years of follow-up [41].

Kidney biopsy is recommended in cases where the cause of CKD is not well defined or accelerated disease progression is observed, or even when the prognosis needs to be defined [7]. According to Wyatt [42], if all PLWH with CKD undergo renal biopsy, the result would show that diabetes and hypertension are the main causes, as in the general population.

The prevalence of hypertension in the population with HIV infection is usually around 25% [43]. Researchers observed that 55% of patients with HIV and CKD were hypertensive and 20% were diabetics [44]. With the increase in life expectancy of individuals with HIV, conditions such as these, closely related to aging, will be increasingly prevalent in this population [38]. Blood pressure should be monitored regularly in patients with HIV, especially in those with a previous diagnosis of CKD. Antihypertensive treatment should be indicated according to individual clinical characteristics, but renin-angiotensin-aldosterone blockade constitutes the baseline therapy in cases with proteinuria.

Although there is no consistent evidence on the role of these treatments in patients with CKD and HIV infection, the recommendations for infected individuals are the same as those for the general population [45] and blood pressure targets may be based on those of other kidney diseases with proteinuria [4].

Patients who are coinfected with HIV and HCV may be at higher risk for kidney disease progression [46]. Researchers have found that in cases of coinfection, a wide variety of clinical renal manifestations were observed, such as hematuria, nephrotic proteinuria (with or without hypercholesterolemia), kidney failure, and hypertension, and histopathological findings, such as membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy with atypical features (including collapsing FSGS, diffuse mesangial proliferation, mesangial deposits, and proliferative and exudative segmental endocapillary glomerulonephritis) [47].

17.6 HIV-Associated Drug Nephrotoxicity

The use of ART in the treatment of HIV infection has a delicate risk–benefit relationship because, although it is associated with increased life expectancy, the renal effects of continuous use of these drugs require strict attention [4]. Research on AKI in PLWH has shown that drugs commonly used to treat the virus-related infections, such as aminoglycoside antibiotics, pentamidine, acyclovir, foscarnet, amphotericin, tenofovir, adefovir, cidofovir, indinavir, atazanavir, sulfadiazine, and sulfamethoxazole-trimethoprim, are likely to be related to nephrotoxicity [48, 49]. However, the results of one study indicated that ART was associated with a slower progression of CKD, as assessed by estimated GFR [50].

In London, between 1998 and 2005, in a cohort of 2274 patients, approximately 6% had at least one episode of AKI during the study period. More than half of the cases occurred during the first 3 months of HIV treatment, and it is possible that AKI was the primary presentation in some patients. When analyzing the study results, the most common factors for the development of AKI were nephrotoxic drugs, opportunistic and non-opportunistic infections, malignancy, and liver disease. A lower CD4 nadir was consistently associated with AKI and HCV coinfection, and intravenous drug use was associated with the onset of this complication after the first 3 months of HIV treatment [24, 51].

In the HAART era, the incidence of AKI in hospitalized patients due to HIV ranged from 6% to 20%, and AKI was associated with an increased in-hospital mortality [52]. In a study of 3329 patients, ART was associated with an increased risk of CKD related to early regimens consisting of tenofovir and ritonavir-boosted protease inhibitor (RTV/PI) [50].

17.7 Acute Interstitial Nephritis

Most cases of acute interstitial nephritis (AIN) are due to drug hypersensitivity. The time of drug exposure shows that AIN can happen within a few days, particularly with reexposure, to weeks or several months. Prior tolerance to certain drugs does not rule out the possibility of it causing interstitial nephritis. Kidney biopsy shows inflammatory interstitial infiltrates with or without interstitial eosinophils [25]. The presence of any degree of kidney failure should raise concerns even in the absence of clinical evidence. On the other hand, even suggestive clinical features often lead to a misdiagnosis [25].

Many drugs can cause AIN, the most common of which include penicillin derivatives, cephalosporins, sulfas, fluoroquinolones, proton-pump inhibitors, and nonsteroidal anti-inflammatory drugs. PLWH may be particularly at risk due to exposure to a large number of drugs. If AIN is suspected, the most common therapeutic approach is to discontinue the probable agent; however, this is not an easy task in the case of patients on multiple-drug regimens. Ideally, if kidney failure persists after drug withdrawal, it is necessary to perform a biopsy. Although studies regarding AIN treatment have not been controlled, corticosteroids may be useful if kidney failure does not improve within a few days to 1 week after withdrawal of the offending drug [25].

The pathogenesis of antiretroviral drug renal toxicity is mainly due to changes in transport protein function in proximal tubule epithelial cells, mitochondrial toxicity, vascular injury, and crystal precipitation at a tubular level. In most cases, the drugs involved in renal toxicity are nucleotide analog reverse transcriptase inhibitors, such as tenofovir and protease inhibitors (PIs).

Some PIs (atazanavir and lopinavir) have been associated with an increased risk of GFR decline, which may be related to the interaction of ritonavir (RTV) with tenofovir when administered concomitantly [45].

Researchers found that the relative risk index (RRI) of tenofovir exposure was 1.32 and 1.18 for indinavir, and atazanavir-adjusted IRR was 1.21. Male gender, older age, low baseline GFR, AIDS during the follow-up, higher viral load, high blood pressure, diabetes, hepatitis C, and cancer without AIDS were independent predictors. The researchers have suggested that long-term renal impairment may be related to different mechanisms, such as tubular and glomerular dysfunction due to tenofovir use, drug crystal accumulations, or renal lithiasis for all three PIs [41].

Tenofovir is currently a component of first-line ART in Brazil and is known for its nephrotoxicity. Eliminated by renal clearance, mainly by glomerular filtration, with 20–30% being actively transported to renal proximal tubular cells, its active uptake occurs in proximal tubule epithelial cells through organic anion transporter 1 (OAT1) channels and, to a lesser extent, OAT3 channels. Tenofovir is then secreted into the tubular lumen via protein 4 associated with multidrug resistance [53]. Approximately 70% of the published cases of nephrotoxic effects induced by this medication occurred with concomitant use of RTV/PI inhibitor [47]. Inhibition of MRP4 by RTV/PI leads to an increase in tenofovir intra-

cellular levels, which may increase its nephrotoxic effects [50, 54, 55]. Increased intracellular drug levels may result in proximal tubular cell injury [56].

In early clinical trials, tenofovir did not seem to cause significant nephrotoxicity. However, with its widespread use, several case reports and observational studies documented its association with nephrotoxicity, as well as the type of AKI, Fanconi syndrome, diabetes insipidus, osteomalacia [57], alterations consistent with acute tubular necrosis, and evidence of mitochondrial injury on biopsy [58].

Complete or partial recovery of renal function is common when tenofovir is discontinued, although recovery time may vary from months to 1 or 2 years [56]. Therefore, patients using tenofovir should be advised of the need for regular monitoring of renal function and urinalysis [59].

Fanconi syndrome is characterized by dysfunction of the proximal tubular cells (widespread resorption impairment), with urinary loss of phosphate, calcium, urate, amino acids, glucose, and bicarbonate. It can manifest as disproportionate phosphaturia and uricosuria, with the development of hypophosphatemia and hypouricemia, aminoaciduria, and glycosuria despite normoglycemia and type II renal tubular acidosis (metabolic acidosis with normal anion gap), as well as tubular proteinuria, usually <2 g/day.

In patients with HIV, Fanconi syndrome can be caused by antiretroviral drugs, especially tenofovir, and less frequently by other nucleoside analogs (didanosine and stavudine). Cases have also been described with the use of adefovir (used for hepatitis B virus infection) and cidofovir (used for cytomegalovirus infection) [20].

Other drugs used to treat HIV are also associated with kidney injury, such as indinavir, which is a protease inhibitor that can cause crystalluria and AKI [18, 60]. In a study with 240 patients, 8% had urological symptoms and 3% had nephrolithiasis due to indinavir calculi, and of the 142 patients who provided urine samples, 20% had urinary drug crystals [61]. Indinavir has a low solubility (0.03 mg/mL) at a pH of 6.0; however, it is much more soluble at lower pH values (100 mg/mL at pH 3.5) [60]. Research involving individuals with urinary pH >6 showed that they were more likely to have indinavir crystals in the urine [61].

Atazanavir, another protease inhibitor, may also lead to stone formation, although it occurs less frequently [60]. However, some studies have described renal lithiasis associated with this medication [62–64]. Drinking at least 1.5 L of fluid per day should be encouraged among patients taking indinavir and atazanavir as a preventive measure against renal lithiasis [60].

Acyclovir is an antiviral, primarily used to treat herpes simplex and varicella-zoster virus infections, which commonly occurs in patients with HIV. AKI is a well-described side effect of acyclovir, and the most common cause is crystal deposition. Unfortunately, although the side effects of acyclovir are well known, they are often underestimated. AKI secondary to this drug is characterized by a decrease in renal function that usually develops within 12–48 hours after drug administration, indicated by a rapid increase in serum creatinine [65]. Patients may complain of nausea and flank and abdominal pain, probably induced by urinary tract obstruction. Immediate detection of AKI is necessary to prevent morbidity [65].

Acyclovir is rapidly excreted in the urine and has a relatively low solubility [60]. Thus, intravenous therapy, especially if the patient is volume depleted, may lead to deposition of acyclovir crystals in the tubules, resulting in intratubular obstruction and foci of interstitial inflammation [8, 66, 67]. A decline in renal function is usually mild, but may occasionally be severe, with a significant increase in plasma creatinine concentrations in some cases [68, 69].

Oral acyclovir therapy is usually well tolerated due to a slower rate of excretion. The rare reported cases of oral acyclovir-associated AKI were related to the use of excessive doses or in patients with underlying kidney disease or in those with severe volume depletion [70, 71]. Complete recovery typically occurs within 4–9 days after drug discontinuation [60].

Sulfas are widely used drugs to treat opportunistic infections in AIDS patients, especially pneumocystis (sulfamethoxazole-trimethoprim)

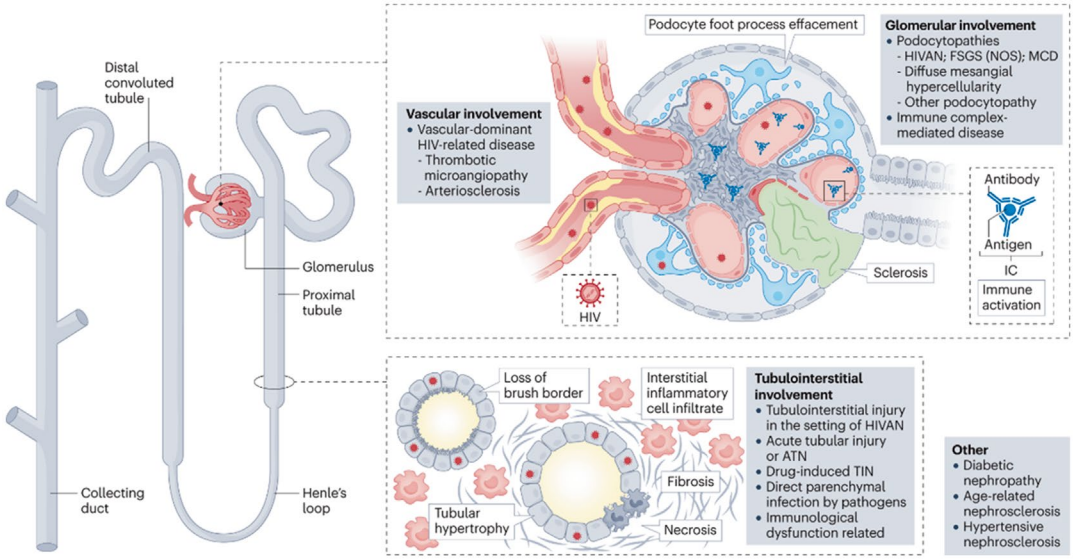


Fig. 17.1 Summarizes the kidney compartments that can be affected by HIV. HIV infection can affect all compartments of the kidney. The pathological classification of HIV-associated kidney diseases proposed by KDIGO is based on the major tissue compartment involved. The four main categories are as follows: glomerular dominant, tubulointerstitial dominant, vascular dominant, and other in the setting of HIV. The schematic view shows the location and subtypes in each main category. ATN, acute tubular injury; FSGS (NOS), focal segmental glomerulosclerosis (not otherwise specified); HIVAN, HIV-associated nephropathy; IC, immune complex; MCD, minimal change disease; TIN, tubulointerstitial nephritis. (Adapted from Diana & Naicker [2])

and toxoplasmosis (sulfadiazine) [26]. Sulfamethoxazole-trimethoprim can cause interstitial nephritis and, more rarely, acute tubular necrosis [72, 73]. Both sulfamethoxazole and sulfadiazine are relatively insoluble in acid urine [60], and intrarenal precipitation of sulfadiazine can result in nephrolithiasis [74].

Considering the abovementioned facts, the importance of careful monitoring of renal function in patients undergoing continuous ART, especially hospitalized patients undergoing therapy with TDF and other nephrotoxic drugs [7], is emphasized.

Figure 17.1 summarizes kidney compartments that can be affected by HIV.

17.8 Kidney Transplantation

Kidney transplantation was not indicated for people living with HIV for many years, and only after 2007 it became an option for HIV-associated end-stage kidney disease [2]. A systematic review and meta-analysis of cohort studies and case series of HIV patients receiving a kidney transplant evidenced good outcomes: patients' survival at 1 year—97%, at 3 years—94%, while graft survival was 91% at 1 year and 81% at 3 years [75]. In this same study, acute rejection was observed in 33% of cases at 1 year and infectious complications in 41% in 1 year [75].

Posttransplant glomerular disease occurs, including new onset or recurrent HIVAN, and factors associated with this complication include APOL1 genetic polymorphism, high viral load, and low CD4 count [76].

17.9 Conclusion

Due to increased access to antiretrovirals, better viral control, and improvement in CD4 T lymphocyte levels, and increased life expectancy of HIV-infected individuals, noncommunicable diseases have become prominent in this population. Increase in morbidity and mortality due to causes

not directly linked to HIV/AIDS, such as hypertension, diabetes, kidney disease, and a decrease in deaths from opportunistic diseases, constitutes the current sequelae of the infection. It is noteworthy that for the control of CKD progression in the HIV population, early identification of kidney injury (through efficient screening), the precise diagnosis (through biopsy, when indicated), renal function monitoring, and appropriate treatment are necessary.

17.10 Take-Home Message

- HIV is still a public health problem, with a higher burden in low and middle-income countries.
- HIVAN, the most specific kidney disease related to HIV, has a strong genetic association with African descent.
- Access to early diagnosis and antiretroviral treatment is crucial to control HIV complications, including kidney injuries, which can manifest in a broad spectrum of diseases.
- Kidney transplant should be considered for HIV patients presenting with advanced chronic kidney disease.

References

1. UNAIDS. Global AIDS Update. Available at https://www.unaids.org/en. Accessed on 24 Sept 2024.
2. Diana NE, Naicker S. The changing landscape of HIV-associated kidney disease. Nat Rev Nephrol. 2024;20(5):330–46.
3. United Nations. Joint United Nations Programme on HIV/AIDS. https://sdgs.un.org/un-system-sdg-implementation/joint-united-nations-programme-hivaids-45799. Accessed on 24 Sept 2024.
4. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. N Engl J Med. 2017;377(24):2363–74.
5. Hadigan C, Edwards E, Rosenberg A, Purdy JB, Fleischman E, Howard L, et al. Microalbuminuria in HIV disease. Am J Nephrol. 2013;37(5)
6. Pinto-Neto LFS, Braga AC, Rocha JA, Vieira NFR, Miranda AE. Fatores de risco associados a alterações renais em pacientes infectados por HIV-1. Rev Soc Bras Med Trop. 2011;44(1):30–4.
7. Swanepoel CR, Atta MG, D'Agati VD, Estrella MM, Fogo AB, Naicker S, et al. Kidney disease in the setting of HIV infection: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int. 2018;93:545–59.
8. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, Aids e Hepatites Virais. Protocolo clínico e diretrizes terapêuticas para manejo da infecção pelo HIV em adultos. 2013. Available at: http://www.aids.gov.br/publicacao/2013/protocolo- clinico-e-diretrizes--terapeuticas-para-manejo-da-infeccao-pelo-hiv-em-adulto. Accessed 10 Aug 2014.
9. World Health Organization (WHO). Policy brief: consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: what's new. 2015. Available at: http://www.who.int/hiv/pub/arv/policy-brief-arv-2015/en/. Accessed 03 May 2018.
10. Estrella MM, Fine DM, Atta MG. Recent developments in HIV-related kidney disease. HIV Ther. 2010;4(5):589–603.
11. Naicker S, Rahmanian S, Kopp JB. HIV and chronic kidney disease. Clin Nephrol. 2015;83(Suppl. 1):S32–8.
12. Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(9):e96–138.
13. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico HIV AIDS 2017. Available at: http://www.aids.gov.br/pt-br/pub/2017/boletim-epidemiologico- hivaids-2017. Accessed: 10 May 2018.
14. Diana NE, Davies M, Mosiane P, Vermeulen A, Naicker S. Clinicopathological correlation of kidney disease in HIV infection pre- and post-ART rollout. PLoS One. 2022;17(5):e0269260.
15. Wearne N, Manning K, Price B, Rayner BL, Davidson B, Jones ES, et al. The evolving spectrum of kidney histology in HIV positive patients in South Africa. Kidney Int Rep. 2023;8(5):1087–96.
16. Kudose S, Santoriello D, Bomback AS, Stokes MB, Batal I, Markowitz GS, et al. The spectrum of kidney biopsy findings in HIV-infected patients in the modern era. Kidney Int. 2020;97(5):1006–16.
17. Levey AS, Levin A, Kellum JA. Definition and classification of kidney diseases. Am J Kidney Dis. 2013;61(5):686–8.
18. Wyatt CM, Klotman PE. Overview of kidney disease in HIV-infected patients. UpToDate. Available at: http://www.uptodate.com. Accessed: 14 May 2018.
19. Wyatt CM, Arons RR, Klotman PE, Klotman ME. Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. AIDS. 2006;20(4):561–5.
20. Silva Junior GB, Daher EF. HIV/SIDA—Complicações renais, distúrbios hidreletrolíticos e ácido-básicos. In: Lopes AC (Org.), editor. Clínica Médica—Diagnóstico e Tratamento, vol. 5. 1ed. São Paulo: Atheneu; 2013. p. 4651–63

21. Winston J, Deray G, Hawkins T, Szczech L, Wyatt C, Young B. Kidney disease in patients with HIV infection and AIDS. Clin Infect Dis. 2008;47:1449–57.
22. Franceschini N, Napravnik S, Eron JJ Jr, Szczech LA, Finn WF. Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. Kidney Int. 2005;67(4):1526–31.
23. Luna LDS, Soares DS, Silva Junior GB, Cavalcante MG, Malveira LRC, Meneses GC, et al. Clinical characteristics, outcomes and risk factors for death among critically ill patients with HIV-related acute kidney injury. Rev Inst Med Trop Sao Paulo. 2016;58:52.
24. Kalim S, Szcech LA, Wyatt CM. Acute kidney injury in HIV-infected patients. Semin Nephrol. 2008;28(6):556–62.
25. Fine DM, Perazella MA, Lucas GM, Atta MG. Renal disease in patients with HIV infection epidemiology, pathogenesis and management. Drugs. 2008;68(7):963–80.
26. Atta MG. Diagnosis and natural history of HIV-associated nephropathy. Adv Chronic Kidney Dis. 2010;17(1):52–8.
27. Friedman DJ, Ma L, Freedman BI. Treatment potential in APOL1-associated nephropathy. Curr Opin Nephrol Hypertens. 2022;31(5):442–8.
28. Abdu A, Duarte R, Dickens C, Dix-Peek T, Bala SM, Ademola B, Naicker S. High risk APOL1 genotypes and kidney disease among treatment naïve HIV patients at Kano, Nigeria. PLoS One. 2022;17(10):e0275949.
29. Sinclair M, Wyatt MC. Regional and racial disparities in HIV-related kidney disease. Contrib Nephrol. 2021;199:106–13.
30. Medapalli RK, He JC, Klotman PE. HIV-associated nephropathy: pathogenesis. Curr Opin Nephrol Hypertens. 2011;20(3):306–11.
31. Becker S, Fusco G, Fusco J, Balu R, Gangjee S, Brennan C, et al. HIV-associated thrombotic microangiopathy in the era of highly active antiretroviral therapy: an observational study. Clin Infect Dis. 2004;39(Suppl 5):267–75.
32. D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011;365:2398–411.
33. Disease K. Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
34. Balow JE. Nephropathy in the context of HIV infection. Kidney Int. 2005;67:1632.
35. Egbuna O, Zimmerman B, Manos G, Fortier A, Chirieac MC, Dakin LA, et al. Inaxaplin for proteinuric kidney disease in persons with two APOL1 variants. N Engl J Med. 2023;388(11):969–79.
36. Bello AK, Levin A, Tonelli M, Okpechi IG, Feehally J, Harris D, et al. Global kidney health atlas: a report by the International Society of Nephrology on the current state of organization and structures for kidney care across the globe. Brussels: International Society of Nephrology; 2017.
37. Sociedade Brasileira de Nefrologia (SBN). Censo 2017. Available at: http://www.censo-sbn. org.br/censosAnteriores. Accessed: 1 may 2018.
38. Ekrikpo UE, Kengne AP, Bello AK, Effa EE, Noubiap JJ, Salako BL, et al. Chronic kidney disease in the global adult HIV-infected population: a systematic review and meta-analysis. PLoS One. 2018;13(4):e0195443.
39. Jo JY, Ryu SA, Kim JI, Lee EH, Choi IC. Comparison of five glomerular filtration rate estimating equations as predictors of acute kidney injury after cardiovascular surgery. Sci Rep. 2019;9(1):11072.
40. Kirsztajn GM, Silva Junior GB, Silva AQB, Abensur H, Romão Junior JE, Bastos MG, et al. Estimated glomerular filtration rate in clinical practice: Consensus positioning of the Brazilian Society of Nephrology (SBN) and Brazilian Society of Clinical Pathology and Laboratory Medicine (SBPC/ML). J Bras Nefrol. 2024;46(3):e20230193.
41. Kirk O, Mocroft A, Reiss P, De Wit S, Sedlacek D, Beniowski M, et al. Chronic kidney disease and exposure to ART in a large cohort with long-term follow-up: the EuroSIDA study. In: Program and abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, U.S; 16–19 Feb 2010. Abstract 107LB.
42. Wyatt CM. The kidney in HIV infection: beyond HIV-associated nephropathy. Top Antivir Med. 2012;20(3):106–10.
43. Nuesch R, Wang Q, Elzi L, Bernasconi E, Weber R, Cavassini M, et al. Risk of cardiovascular events and blood pressure control in hypertensive HIV-infected patients: Swiss HIV Cohort Study (SHCS). J Acquir Immune Defic Syndr. 2013;62(4):396–404.
44. Wyatt CM, Winston JA, Malvestutto CD, Fishbein DA, Barash I, Cohen AJ, et al. Chronic kidney disease in HIV infection: an urban epidemic. AIDS. 2007;21(15):2101–3.
45. Górriz JL, Gutiérrez F, Trullas JC, Arazo P, Arribas JR, Barril G, et al. Documento de con- senso sobre el manejo de la patología renal en pacientes con infección por VIH. Nefrologia. 2014;34(Suppl.2):1.
46. Kamar N, Rostaing L. Renal disease associated with hepatitis C virus infection. UptoDate. 2014. Available at http://www.uptodate.com. Accessed 28 Sept 2014.
47. Cheng JT, Anderson HL, Markowitz GS, Appel GB, Pogue VA, D'Agati VD. Hepatitis C virus-associated glomerular disease in patients with human immunodeficiency virus coinfection. J Am Soc Nephrol. 1999;10:1566–74.
48. Kalyesubula R, Perazella MA. Nephrotoxicity of HAART. AIDS Res Treat. 2011; Article ID 562790, 11.
49. Friedl DB, Aprile DCB, Fino LC, Barbosa DA, Belasco AGS. Evolução da função renal de pacientes portadores do Vírus da Imunodeficiência Humana/Síndrome da Imunodeficiência Adquirida. Acta Paul Enferm. 2009;22(Especial-Nefrologia):531–4.
50. Kalayjian RC, Lau B, Mechekano RN, Crane HM, Rodriguez B, Salata RA, et al. Risk factors for chronic

kidney disease in a large cohort of HIV-1 infected individuals initiating antiretro- viral therapy in routine care. AIDS. 2012;26(15):1907–15.
51. Roe J, Campbell LJ, Ibrahim F, Hendry BM, Post FA. HIV care and the incidence of acute renal failure. Clin Infect Dis. 2008;47:242–9.
52. Lopes JA, Melo MJ, Raimundo M, Fragoso A, Antunes F. Long-term risk of mortality for acute kidney injury in HIV-infected patients: a cohort analysis. BMC Nephrol. 2013;14:32.
53. Kiertiburanakul S, Chaisiri K, Kasettratat N, Visuttimak P, Bowonwatanuwong C. Monitoring of renal function among HIV-infected patients receiving tenofovir in a resource-limited. J Int Assoc Phys AIDS Care. 2011;10(5):297–302.
54. Imaoka T, Kusuhara H, Adachi M, Schuetz JD, Takeuchi K, Sugiyama Y. Functional involvement of multidrug resistance-associated protein 4 (MRP4/ABCC4) in the renal elimination of the antiviral drugs adefovir and tenofovir. Mol Pharmacol. 2007;71(2):619–27.
55. Ray AS, Cihlar T, Robinson KL, Tong L, Vela JE, Fuller MD, et al. Mechanism of active renal tubular efflux of tenofovir. Antimicrob Agents Chemother. 2006;50(10):3297–304.
56. Jao J, Wyatt CM. Antiretroviral medications: adverse effects on the kidney. Adv Chronic Kidney Dis. 2010;17(1):72–82.
57. Gitman MD, Hirschwerk D, Baskin CH, Singhal PC. Tenofovir-induced kidney injury. Expert Opin Drug Saf. 2007;6:155–64.
58. Herlitz LC, Mohan S, Stokes MB, Radhakrishnan J, D'Agati VD, Markowitz GS. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. Kidney Int. 2010;78(11):1171.
59. Bartlett JG. Counseling HIV-infected patients regarding potential side effects of antiretroviral therapy. UpToDate 2013. Available at http://www.uptodate.com. Accessed 28 Sept 2014.
60. Perazella MA. Crystal-induced acute kidney injury (acute renal failure). UpToDate 2014. Available at http://www.uptodate.com. Accessed 28 Sept 2014.
61. Kopp JB, Miller KD, Mican JAM, Feuerstein IM, Vaughan E, Baker C. Ann Intern Med. 1997;127(2):119–25.
62. Couzigou C, Daudon M, Meynard JL, Borsa-lebas F, Higueret D, Escaut L, et al. Urolithiasis in HIV-positive patients treated with atazanavir. Clin Infect Dis. 2007;45(8):e105–8.
63. Chan-tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's adverse event reporting system. AIDS. 2007;21(9):1215–8.
64. Nadler RB, Rubenstein JN, Eggener SE, Loor MM, Smith ND. The etiology of urolithiasis in HIV infected patients. J Urol. 2003;169(2):475–7.
65. Fleischer P, Johnson M. Acyclovir nephrotoxicity: a case report highlighting the importance of prevention, detection, and treatment of acyclovir-induced nephropathy. Case Rep Med. 2010; https://doi.org/10.1155/2010/602783.
66. Berns JS, Cohen RM, Stumacher RJ, Rudnick MR. Renal aspects of therapy for human immunodeficiency virus and associated opportunistic infections. J Am Soc Nephrol. 1991;1(9):1061–80.
67. Sawyer MH, Webb DE, Balow JE, Straus SE. Acyclovir-induced renal failure. Clinical course and histology. Am J Med. 1988;84(6):1067–71.
68. Krieble BF, Rudy DW, Glick MR, Clayman MD. Case report: acyclovir neurotoxicity and nephrotoxicity—the role for hemodialysis. Am J Med Sci. 1993;305(1):36–9.
69. Obada EN, Level G, Mathieu P, Parent X, Gilson B, Bindi P. Acute renal failure following a treatment with acyclovir. Nephrol Ther. 2010;6(2):125–7.
70. Eck P, Silver SM, Clark EC. Acute renal failure and coma after a high dose of oral acyclovir. N Engl J Med. 1991;325(16):1178–9.
71. Giustina A, Romanelli G, Cimino A, Brunori G. Low-dose acyclovir and acute renal failure. Ann Intern Med. 1988;108(2):312.
72. Domingo P, Ferrer S, Cruz J, Morla R, Ris J. Trimethoprim-sulfamethoxazole-induced renal tubular acidosis in patient with AIDS. Clin Infect Dis. 1995;20(5):1435–7.
73. Hemstreet BA. Antimicrobial-associated renal tubular acidosis. Ann Pharmacother. 2004;38(6):1031–8.
74. Hein R, Brunkhorst R, Thon WF, Schedel I, Schmidt RE. Symptomatic sulfadiazine crystalluria in AIDS patients: a report of two cases. Clin Nephrol. 1993;39(5):254–256.
75. Zheng X, Gong L, Xue W, Zeng S, Xu Y, Zhang Y, Hu X. Kidney transplant outcomes in HIV-positive patients: a systematic review and meta-analysis. AIDS Res Ther. 2019;16(1):37.
76. Muller E, Botha FCJ, Barday ZA, Manning K, Chin-Hong P, Stock P. Kidney Transplantation in HIV-positive Patients: Current Practice and Management Strategies. Transplantation. 2021;105(7):1492–501.

18 Viral Hepatitis and Kidney Disease

Elodie Bomfim Hyppolito, Roberto da Justa Pires Neto, and Geraldo Bezerra da Silva Junior

18.1 Introduction

Viral hepatitis is a generic term that defines the condition characterized by damage to the liver, especially the hepatocyte, caused by viruses. There are many families of viruses capable of causing damage to the hepatocyte: *Flaviviridae* (hepatitis C, yellow fever, dengue), *Herpesviridae* (cytomegalovirus, Ebstein-Barr), *Hepadnaviridae* (hepatitis B), *Picornaviridae* (hepatitis A), among others. However, some of these infectious agents cause self-limiting acute damage, leading to temporary clinical manifestations, often evolving to spontaneous cure, as is the case with infection by the hepatitis A and E viruses. Other infectious agents, especially the hepatitis B, hepatitis D, and hepatitis C viruses, in addition to acute damage, can evolve to chronic infection with variable consequences. Recently, the possibility of chronic hepatitis E virus (HEV) in immunosuppressed individuals such as HIV carriers and organ transplant recipients has been described [1]. This chapter emphasizes the presentation of kidney alterations caused by hepatotropic viruses A, B, C, D, and E.

E. B. Hyppolito
Medicine Course, University of Fortaleza, Fortaleza, Ceara, Brazil

São José Hospital for Infectious Diseases, Ceara State Health Department, Fortaleza, Ceara, Brazil

R. da Justa Pires Neto
Department of Community Health, School of Medicine, Federal University of Ceara, Fortaleza, Ceara, Brazil
e-mail: robertojusta@ufc.br

G. Bezerra da Silva Junior (✉)
Post-Graduation Programs in Public Health and Medical Sciences, School of Medicine, University of Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

18.2 Hepatitis A

18.2.1 The Virus (HAV)

HAV was characterized in 1973. It is a positive-sense RNA virus in the *Herpavirus* genus of the *Picornaviridae family*, with four genotypes characterized in humans. It is a small, non-enveloped particle (27 nm) in an icosahedral shape [2].

18.2.2 Epidemiology

HAV is transmitted by the fecal-oral route between people in close contact with each other. HAV from contaminated food and water usually infects individuals who have not washed their hands properly after defecation. Fresh produce may be a culprit in the spread of HAV infection because the virus is difficult to remove from the surfaces of fruits and vegetables. Transient viremia after initial acquisition accounts for the

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_18

rarely observed parenteral transmission. Risk factors in developed countries include men who have sex with men (MSM), travel to an endemic country, and intravenous drug use [2].

An estimated 1.4 million cases of hepatitis A occur globally each year, with variation depending on socioeconomic status and access to drinking water. In developing countries with poor sanitation, almost the entire population is seropositive for HAV immunoglobulin G (IgG) [3]. The number of reported cases of hepatitis A in children has been decreasing since 2015; however, there has been a relative increase in the number of reported cases in adults and special populations, such as men who have sex with men. The northern and northeastern regions account for 55% of the reports of this condition in SINAN [1].

18.2.3 Natural History

The hepatitis A virus reaches the liver through the portal vein, after crossing the mucosa of the small intestinal vessels. The viral particles then replicate and are secreted into the bile canaliculi, returning to the intestine through the bile ducts and being re-excreted in the feces. Until the body responds with the appropriate immune reaction, with the production of antibodies, the enterohepatic cycle of hepatitis A continues [4]. Virus-specific CD8+ T lymphocytes, restricted to human leukocyte antigen, and natural killer cells have been implicated as responsible for the damage and destruction of infected hepatocytes [4]. Clinical progression is associated with the age at which the infection is acquired. In young people, hepatitis A is usually asymptomatic or mildly symptomatic, but in people over 50 years of age, the disease can be more symptomatic and severe [5]. Hepatitis A does not cause chronic disease.

18.2.4 Clinical Manifestations

Hepatitis A has an incubation period of approximately 2–4 weeks. In most cases, it is a benign, self-limiting acute disease, and fulminant hepatitis rarely occurs [5]. The most common symptoms include fever, malaise, and jaundice [4]. The disease usually begins with a prodromal course of constitutional and gastrointestinal symptoms [5]. Other frequent manifestations are as follows: weakness, fatigue, nausea, vomiting, abdominal pain (mostly located in the right hypochondrium), arthralgias, myalgias, diarrhea, and anorexia [4]. After a few days, jaundice appears, associated with choluria, fecal hypocholia, and pruritus [5]. Liver enzymes are usually above 1000 IU/dL, associated with increased total bilirubin, but below 10 mg/dL, and alkaline phosphatase less than 400 IU/L. Usually, alanine aminotransferase (ALT/TGO) is higher than aspartate aminotransferase (AST/TGP) [4].

18.2.5 Kidney Involvement

Kidney involvement in hepatitis A has been little studied. Acute kidney injury (AKI) is common in fulminant hepatitis A and is described in cases without fulminant hepatitis in less than 5% of cases [5]. A study of 446 patients with hepatitis A in Seoul, Korea, showed AKI in 21 patients (4.7%). Six of the 21 patients with AKI (29%) required hemodialysis, with recovery of kidney function after the acute hepatitis episode. Kidney biopsy was performed in two cases, showing acute tubular necrosis and interstitial nephritis [6]. In another study evaluating patients undergoing liver transplantation, patients who had hepatitis A and AKI had higher levels of prothrombin time and serum creatinine in the preoperative period of the transplant, despite lower levels of bilirubin [7]. Predictors of AKI in hepatitis A include reduced cholesterol and albumin levels and elevated ALT and C-reactive protein levels [5].

18.2.6 Treatment

There is no specific treatment for hepatitis A. The use of alternative medicine, such as teas and other substances of unknown plant origin, is not recommended, as there are reports of serious complications caused by possible hepatotoxic

substances [5]. In addition, there are natural substances, including herbs, with nephrotoxic potential [8].

18.3 Hepatitis B

18.3.1 The Virus (HBV)

Viral hepatitis B is caused by a DNA virus belonging to the *Hepadnaviridae family*. The hepatitis B virus (HBV) is a representative of this family, which has as a common characteristic an incomplete double-stranded DNA whose replication occurs through the action of the enzyme reverse transcriptase [9, 10]. HBV is considered an oncogenic virus and has ten genotypes, classified from A to J. Some HBV genotypes are classified into subgenotypes. More than 30 subgenotypes have been identified. In Brazil, the predominance of subgenotypes A1, A2, F2a, and F4 is observed [11, 12, 13].

18.3.2 Epidemiology

Contagion through unprotected sexual intercourse is the main form of transmission of hepatitis B. In addition to this form, hepatitis B is also a disease of parenteral transmission. Transmission can also occur through a break in continuity (skin and mucous membranes) and parenteral transmission (sharing needles, syringes, manicure and pedicure equipment, razors and waxing blades, tattoos, piercings, dental or surgical procedures that do not meet biosafety standards, among others). Vertical transmission (mother-child) is also important and associated with an unfavorable evolution, with a greater chance of chronicity. HBV remains viable for a long period when outside the body and has a greater chance of infecting a susceptible individual than the hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Other body fluids, such as semen, vaginal secretion, and breast milk, can also contain the virus and represent sources of infection [9, 10, 14–16].

In 2006, it was estimated that 2 billion people had been infected with HBV and that 360 million people were living with chronic hepatitis B worldwide. There is geographic variation in the prevalence of hepatitis B. Endemic regions such as Southeast Asia, sub-Saharan Africa, and parts of South America have prevalence rates greater than 8% compared with 2% in non-endemic areas, including most of North America. Routes of transmission differ between endemic and non-endemic areas and determine the course of HBV infection. In endemic areas, vertical mother-to-child transmission and horizontal transmission among young children are the most common routes of HBV infection, but in non-endemic areas, intravenous drug use and sexual transmission in adults are the predominant modes of infection. Severely infected adults with intact immune systems, however, spontaneously resolve HBV infection in up to 95% of cases. The prevalence of hepatitis B globally varies inversely with the availability of vaccination [17].

18.3.3 Natural History

HBV infection can cause acute or chronic hepatitis. Both forms are usually oligosymptomatic, that is, they have few or no characteristic symptoms. Infections caused by the hepatitis B virus rarely cause jaundice, and less than one-third of infected individuals present this clinical sign. Approximately 5–10% of infected individuals become chronic carriers of HBV. Approximately 20–25% of chronic cases of hepatitis B that present replication of the virus progress to advanced liver disease. HBV infection is also a condition for the development of Delta hepatitis, a disease resulting from HDV infection that has a major impact on the Amazon region [9, 10].

In adults exposed exclusively to HBV, spontaneous cure occurs in approximately 90% of cases. Progression to chronic infection, in turn, occurs to a lesser extent and is defined as the persistence of the virus or the presence of HBsAg for more than 6 months, detected by serological tests [9, 10].

Extremes of age and other behavioral and genetic factors, demographic characteristics, or concomitant use of toxic substances, including alcohol and smoking; family history of hepatocellular carcinoma (HCC); and contact with carcinogens such as aflatoxins, for example, increase the risk of liver cirrhosis and HCC in patients with chronic hepatitis B. Persistent viral replication, the presence of cirrhosis, HBV genotype C, mutation in the pre-core promoter region, and coinfection with HIV or HCV are also factors that increase the likelihood of progression to severe forms. Although cirrhosis is a risk factor for HCC, 30–50% of HCC cases caused by HBV occur in the absence of cirrhosis [9, 10].

18.3.4 Clinical Manifestations

HBV infection is a dynamic process and is divided into five phases. The first phase, called immunotolerant, is characterized by high viral replication, with no evidence of hepatocellular aggression. The term immunotolerance phase is due to the fact that viral replication is tolerated by the host's immune system. Thus, this phase is characterized by HBeAg positivity, high serum HBV DNA levels, normal or near-normal aminotransferase levels, little necroinflammatory activity in the liver, and slow progression of fibrosis. This phase is generally longer in individuals infected by vertical transmission. Due to high viremia, patients in this phase can transmit the disease more easily. In a subsequent phase, immunoreactive, immunological tolerance is exhausted, the HBeAg test appears reactive, and serum HBV DNA levels are lower, indicating lower viral replication. Aminotransferase values may fluctuate, and necroinflammatory activity in the liver, in turn, may be moderate or severe. The progression of fibrosis is accelerated. This phase can last from several weeks to several years and is reached more quickly by individuals infected in adulthood. It ends with seroconversion to anti-HBe [5].

The inactive carrier state phase is characterized by very low or even undetectable levels of serum HBV DNA, with normalization of aminotransferases and, usually, anti-HBe seroconversion. In this situation, the host's immune system is able to repress viral replication, reducing the risk of cirrhosis and HCC. This process corresponds to a good prognosis [5].

The reactivation phase may occur after the inactive period, when mutations occur in the precore and/or core-promoter region of the virus, maintaining viral replication even in the presence of nonreactive HBeAg. Necroinflammatory activity and fibrosis in the liver persist during this phase. Chronic hepatitis B with nonreactive HBeAg is also associated with low rates of spontaneous remission and a high risk of complications, such as decompensated cirrhosis and HCC. Even after an immune response with elimination of HBsAg, there is the possibility of low viral replication (undetectable or very low levels of serum HBV DNA). This is the phase called negative HBsAg (nonreactive). There is little information about the importance of this hidden and persistent infection, but it is understood that reactivation may occur in patients with an atypical serological profile, characterized by the presence of reactive anti-HBc, regardless of reactivity to anti-HBs [9, 10].

18.3.5 Kidney Involvement

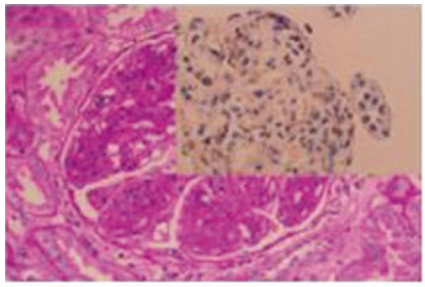
The main kidney manifestation of hepatitis B virus infection is glomerulonephritis, which is more common in children and males. In children, the disease usually has a better prognosis than in adults, progressing with remission of proteinuria after viral clearance. Adults often develop persistent proteinuria and chronic kidney disease, in 25–35% of cases [18]. The most common histological types are membranous and membranoproliferative glomerulonephritis [20]. IgA nephropathy and focal segmental glomerulosclerosis have also been described [21].

The genesis of HBV kidney injury involves direct injury by the virus, cytopathic action of viral proteins on glomerular and tubular cells, immune mechanisms mediated by viral antigens deposited in glomerular structures, and tissue injury by deposition of immune complexes, including in the glomerular capillary wall. All of

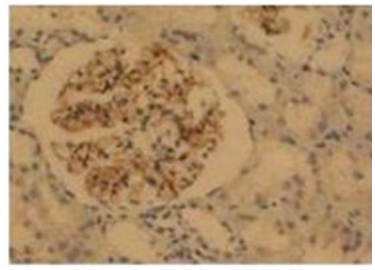
these mechanisms are almost always associated with the production of cytokines and inflammatory mediators, which amplify kidney injury [18, 21]. There is also a genetic predisposition, since an association between kidney disease caused by the hepatitis B virus and some types of HLA has been demonstrated [20]. The main mechanism described for kidney injury caused by the hepatitis B virus is the deposition of immune complexes in the glomeruli. These immune complexes are formed by viral antigens and can be formed in situ or in the circulation. Several antigens have been demonstrated in the glomeruli of patients with hepatitis B-associated glomerulonephritis, including HBsAg, HBeAg, and HBcAg [20]. Immune complex deposits occur predominantly in the subepithelial region but occasionally occur in the mesangial and subendothelial regions. There is also evidence of induction of apoptosis in hepatitis B, which would be related to tubular injury and kidney fibrosis [20].

The most common kidney lesion in hepatitis B is membranous nephropathy, accounting for 10–15% of cases of membranous nephropathy in adults in regions where hepatitis B is endemic [19]. Membranous nephropathy is characterized by mesangial hypercellularity and endocapillary proliferation [22] (Fig. 18.1). Immunofluorescence shows deposition of IgG, IgM, C3, kappa, and lambda in the mesangial region, with a granular pattern, and electron microscopy shows subepithelial, endothelial, and mesangial deposits and immune complexes. It usually manifests with proteinuria, which can reach nephrotic levels, associated with microscopic hematuria in some cases. Loss of kidney function can also be found but is more frequent in membranoproliferative glomerulonephritis. In children, it is common to observe spontaneous remission of proteinuria in membranous nephropathy, compared to adults. There is also a positive association between worsening of liver conditions and progression of kidney disease in hepatitis B, which may be associated with cryoglobulinemia [20].

Membranoproliferative glomerulonephritis is the most frequently associated with HBV infection, characterized by lobular accentuation of the glomerular tuft, duplication of the glomerular basement membrane ("train track" pattern), and deposition of IgG, C3, kappa, and lambda in immunofluorescence. Electron microscopy can detect subepithelial, subendothelial, and mesangial immune complex deposits [18]. In membranoproliferative glomerulonephritis, varying degrees of proteinuria occur, usually in the con-



Mesengloproliferative GN with hepatitis B surface antigen positivity on IHC



Membranoproliferative GN hepatitis B core antigen

Fig. 18.1 Renal histopathological findings associated with hepatitis B. Membranoproliferative glomerulonephritis and immunohistochemistry showing hepatitis B virus antigens. (©2018 John Wiley and Sons, reproduced with permission from Shah & Amarapurkar et al. [22])

text of nephritic syndrome, with consumption of complement, C3, and C4 fractions [19].

A rare but serious manifestation of chronic HBV infection is polyarteritis nodosa, which manifests with skin lesions (erythematous nodules, purpura, *livedo reticularis*, ulcers, blisters), nephropathy, fever, weight loss, hypertension, abdominal pain, neuropathy, myopathy, and coronary artery disease. Kidney injury is characterized by vascular injury with varying degrees of fibrinoid necrosis, fibrin deposition, and leukocyte infiltration in the vessel walls, with the glomeruli being relatively preserved [18].

Some comorbidities frequently found in patients with hepatitis B (diabetes, hypertension, HIV, hepatitis C), as well as the use of other potentially nephrotoxic medications, including aminoglycosides and nonsteroidal anti-inflammatory drugs, may contribute to the development of kidney damage during treatment of hepatitis B [21].

Biopsy findings in hepatitis B-associated membranous nephropathy demonstrate thickening of the capillary wall and glomerular basement membrane on light microscopy, granular deposits of IgG, C3, and IgM in the subepithelial region of the glomerular basement membrane, associated with extensive podocyte damage, and the presence of viral particles in several locations throughout the glomeruli. In membranoproliferative glomerulonephritis, mesangial proliferation is observed, with thickening of the capillary walls resulting in a lobular appearance of the glomerular tuft. The capillary wall may also demonstrate a double contour and hypercellularity, with infiltration of monocytes and neutrophils. Granular deposits of IgG, complement components, and IgM are observed on immunofluorescence in the subendothelial, mesangial, and paramesangial regions [20].

The specific treatment used in hepatitis B can cause kidney damage, mainly causing tubular and hydroelectrolytic disorders, including hypophosphatemia, proximal tubulopathy, and renal acidosis [21].

Nucleotide analogues are associated with nephrotoxicity related to the cumulative effect of their metabolites on renal tubular cells, being more frequent with cidofovir compared with adefovir, which in turn is more nephrotoxic than tenofovir [21]. The inhibition of mitochondrial DNA replication caused by these drugs, leading to dysregulation of mitochondrial respiratory function at the level of epithelial cells of the proximal renal tubule, is the main known mechanism of action.

Nucleoside analogues are generally considered non-nephrotoxic. This evidence emerges in part due to extensive experience with the use of LAM in HIV-infected patients. In these patients, only rare cases of LAM-induced tubular dysfunction have been reported. Entecavir, in turn, is also considered non-nephrotoxic, with rare reports of lactic acidosis [21].

HBV infection in kidney transplant recipients may occur as a new infection or recurrence in patients with chronic infection, cholestatic hepatitis, chronic hepatitis, cirrhosis, or hepatocellular carcinoma [20]. Screening for viral hepatitis should be routine in kidney transplant patients, from preparation to posttransplantation. Regular testing of α-fetoprotein and liver ultrasound are essential for early detection of liver carcinoma, which provides a better prognosis. In the past, the incidence of chronic hepatitis in kidney transplant recipients reached 80%, with a mortality of approximately 60% due to liver complications. Monitoring of kidney transplant recipients with positive viral serologies should be performed continuously for early diagnosis of liver complications, including liver dysfunction and hepatocarcinoma [20].

The use of kidneys from HBsAg-positive carriers for donation and transplantation has been the subject of discussion and controversy. Precautions to avoid transmission to the recipient through the graft should be taken, including prior vaccination and use of anti-HBV immunoglobulin during surgery and possibly in the late postoperative period.

18.3.6 Treatment

The list of drugs used for the specific treatment of chronic hepatitis B is composed of lamivudine

(LAM), adefovir, cidofovir, entecavir (ETV), telbivudine (LDT), emtricitabine, tenofovir (TDF), conventional interferon (INF) alfa-2a and alfa-2b, and pegylated interferon (peg-INF) alfa-2a and alfa-2b. Lamivudine, adefovir, and cidofovir, as they are drugs with low genetic barriers, are no longer used for the treatment of hepatitis B in Brazil, since their use is associated with the rapid development of HBV resistance. Telbivudine and emtricitabine are not available in Brazil for the treatment of chronic hepatitis B and do not offer superiority when compared to entecavir. INF alfa-2a and alfa-2b (INF), in turn, are also drugs considered obsolete and no longer used in Brazil. TDF and entecavir are the first-line drugs currently used in Brazil for the treatment of chronic hepatitis B. Peg-INF alfa-2a and alfa-2b can be used in specific situations, such as hepatitis B carriers with HBe+ and who do not have contraindications such as cirrhosis, heart disease, or hypothyroidism [10].

Patients with HBV-associated nephropathy should be treated according to the recommended protocol for the treatment of hepatitis B and generally show improvement in nephropathy associated with improvement in the B virus infection. Treatment of hepatitis B nephropathy with specific drugs, such as INF and 3TC, has been successful in reducing proteinuria, especially in children with membranous nephropathy. Treatment with INF for 4–12 weeks has been associated with proteinuria remission rates ranging from 20% to 100% and a reduction in circulating viral antigens by 20% to 80% [18, 20]. Nucleoside and nucleotide analogues, such as 3TC, telbivudine, adefovir, entecavir, and TDF, suppress HBV replication, thus reducing the amount of circulating antigen, which is theoretically beneficial in the treatment of nephropathy associated with viral infection. Nucleoside analogues, such as 3TC, rarely cause kidney injury, characterized by tubular dysfunction [21]. Treatment and monitoring of patients with chronic hepatitis B should always include assessment of kidney function, including estimation of the glomerular filtration rate (GFR) and analysis of urinary sediment, adjusting medication doses whenever necessary, and avoiding the use of nephrotoxic drugs as far as possible, taking into account the risk-benefit ratio.

In the case of polyarteritis nodosa associated with chronic HBV infection, treatment with immunosuppressants is indicated. Specific treatment to reduce proteinuria, with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs), is recommended for all patients, except for contraindications, as it is generally associated with a better prognosis in glomerular diseases [18].

18.4 Hepatitis D

18.4.1 The Virus (VHD)

First described in the 1970s in Italy, the "delta" virus had the peculiarity of being found only in people infected with the hepatitis B virus and was therefore described as a defective RNA virus [5]. The HDV, in coinfection with the B virus, uses its DNA and protein envelope to complete its biological cycle [5].

18.4.2 Epidemiology

There are between 15 and 20 million people with chronic HDV infection worldwide, and of those with hepatitis B virus, 5% have HDV. The regions endemic for HDV are as follows: the Middle East, Central Africa, Southern Europe and the Mediterranean, parts of Asia, the Amazon, Colombia, and Venezuela. In Brazil, currently, 41% and 27% of reported cases are concentrated in the states of Amazonas and Acre, respectively. Between 1999 and 2018, 3,984 confirmed cases of hepatitis D were reported in Brazil.

18.4.3 Natural History

HDV is transmitted parenterally, mainly through needle sharing (drug users) and blood transfusions (increasingly less common). Hepatitis D is one of the most common causes of fulminant hepatitis. The incubation period varies from 3 to

7 weeks, which is characterized by the replication of the virus. The chronic form of hepatitis D is the most severe and the one that progresses the fastest of all viral hepatitis that becomes chronic, causing cirrhosis in 70% of cases [5].

18.4.4 Clinical Manifestations

Hepatitis D can present asymptomatically or as fulminant hepatitis [5]. The initial presentation is characterized by nonspecific symptoms, such as nausea, anorexia, and fatigue, followed by the appearance of jaundice, with hyperbilirubinemia, choluria, and fecal acholia [5]. In patients with chronic hepatitis B, VHD can lead to worsening of the condition and hepatic decompensation.

18.4.5 Kidney Involvement

To date, there are no reports of cases of kidney injury associated with the D virus.

18.4.6 Treatment

To date, no medication has shown efficacy in the treatment of hepatitis D. The only medication approved for use in this disease is interferon-α [5]. The clinical protocol of the Ministry of Health recommends the simultaneous administration of alfa peginterferon and a nucleoside analogue for 48 weeks, renewed for another 48 weeks upon clinical and laboratory evaluation [1].

18.5 Hepatitis C

18.5.1 The Virus (HCV)

Initially called "non-A non-B hepatitis," the etiology of hepatitis C was only elucidated in 1989 [23]. Hepatitis C virus (HCV) is a virus of the *Flaviviridae family*. Phylogenetic analysis subdivides HCV into six main genotypes with important subtypes. The distribution of the various HCV genotypes and subtypes shows significant geographic variation. Genotypes 1, 2, and 3 are predominantly found in Europe, Japan, and the United States; genotype 4 is found mainly in Egypt and Zaire; genotype 5 in South Africa; and genotype 6 in Asia. In 2018, a new study classified HCV into 8 genotypes [24].

18.5.2 Epidemiology

Hepatitis C is a disease that affects between 80 and 150 million people worldwide [25], approximately 3% of the global population, and is one of the main causes of liver transplants. It is transmitted mainly parenterally, through contact with contaminated blood [5]. Sexual transmission of HCV has also been reported sporadically in some population groups [26–28]. Vertical transmission is also possible.

In Brazil, hepatitis C was mainly transmitted through injectable drug use, hemodialysis, blood transfusions and blood products, and other invasive medical procedures, especially until the early 1990s. Parenteral transmission through the systematic administration of multivitamins in glass syringes was particularly important among athletes until the 1980s. Currently, people who use drugs, whether injectable or inhaled, still constitute a risk group in Brazil, although in much smaller numbers than in Asia, Europe, and the United States. However, transmission of the virus was not restricted to these groups. Other transmission mechanisms have been identified: manicure and pedicure procedures, piercings and tattoos, dental treatments, use of glass syringes, upper digestive endoscopy, and unprotected sexual intercourse [29]. The disease has also found opportunities to spread in populations that present additional vulnerability factors, such as mental disorders and deprivation of liberty. It is estimated that there are between 1.4 and 1.7 million people chronically infected with HCV in Brazil. Most people with hepatitis C are unaware of their diagnosis, and few know how the disease was transmitted or that there is treatment for the disease. In Brazil, approximately 10,000 cases are reported each year [1].

The epidemiology of hepatitis C is not homogeneous in our country. Regions where injectable drug use was frequent also have a higher number of people chronically infected with HCV [1]. A population-based study on infections by hepatitis A, B, and C viruses in Brazilian capitals found the following prevalences of Anti-HCV: 2.1% in the North Region, 0.7% in the Northeast, 1.3% in the Central-West Region, 1.3% in the Southeast Region, 1.2% in the South Region, and 0.8% in the Federal District. The most relevant risk factor found in the population aged 13–69 years was drug use [1, 30]. From 1999 to 2015, 289,459 cases of hepatitis C were reported in Brazil. Of the total number of cases reported during this period, 64.2% were concentrated in the Southeast region, 24.2% in the South region, 5.6% in the Northeast region, 3.2% in the Central-West region and 2.7% in the, North region. Among the confirmed cases of hepatitis C, approximately 150,000 cases (58.8%) occurred among men and 41.2% among women. Of the total number of confirmed cases of hepatitis C between 2007 and 2015 (approximately 120,000 individuals), 10% were coinfected with HIV. However, over these years, there has been a reduction in the percentage of coinfected individuals, which in 2007 represented 14.4% and, in 2015, represented 9.0% [1, 30].

18.5.3 Natural History

The natural history of hepatitis C is marked by a silent evolution. The signs and symptoms are common to other chronic parenchymal liver diseases and usually only appear in the most advanced stages of the disease. Thus, most cases are asymptomatic, and the diagnosis of the disease is usually late, occurring decades after the viral infection. Due to the progression of the disease and its complications, which require specialized healthcare, hepatitis C represents a significant impact on public health [5].

Hepatocellular aggression caused by HCV can result in liver fibrosis, cirrhosis, and liver cancer. In advanced stages of the disease, the patient may die [5]. It is estimated that hepatitis C is responsible for approximately 700,000 deaths annually as a result of its complications, especially cirrhosis and liver cancer.

18.5.4 Clinical Manifestations

In general, acute viral hepatitis C presents a subclinical course. Approximately 80% of cases are asymptomatic and anicteric, which makes diagnosis difficult. A small proportion of patients eventually present with jaundice (<10%), while no more than 20% present with more intense nonspecific symptoms, such as anorexia, asthenia, malaise, and abdominal pain. When these nonspecific symptoms are present, differential diagnosis is only possible by performing rapid or serological tests to detect antibodies [31, 32].

Symptoms of acute infection may begin between 6 and 20 weeks after exposure to HCV. The acute phase of hepatitis C may last up to six months, but it usually resolves by the 12th week. This phase is characterized by elevated serum aminotransferases, especially alanine aminotransferase (ALT), which increases between 2 and 8 weeks after exposure, indicating hepatocyte necrosis, and may be accompanied by nausea, vomiting, fatigue, low-grade fever, and headache. Other clinical manifestations may subsequently appear, such as abdominal pain, jaundice, pruritus, choluria, acholia, and arthralgia [5]. In self-limited acute hepatitis C, which occurs in 15–25% of cases, symptoms may persist for weeks. Acute HCV infection may be severe, but fulminant liver failure is rare. Spontaneous viral clearance after acute HCV infection occurs in 25–50% of cases. Some host factors are associated with spontaneous viral elimination, such as age under 40 years, female sex, appearance of jaundice, and genetic factors such as interleukin-28B (IL28B) CC polymorphism [33, 34].

Hepatitis C is usually diagnosed in its chronic phase. Since symptoms are often scarce and nonspecific, the disease evolves for decades without diagnosis. In general, diagnosis occurs after routine serological testing or blood donation. This fact reiterates the importance of clinical suspi-

cion by the entire multidisciplinary team and of increasing the availability of serological diagnosis, especially for populations vulnerable to HCV [35]. In most people infected with HCV, the first two decades after transmission are characterized by insidious and asymptomatic evolution [36]. Serum levels of ALT show intermittent elevations in 60–70% of those with chronic infection [5]. In the most severe cases, progression to cirrhosis and hepatic decompensation occurs, characterized by systemic changes and portal hypertension, evolving with ascites, esophageal varices, and hepatic encephalopathy.

In the absence of treatment, 60–85% of cases become chronic; on average, 20% may progress to cirrhosis, and 1–5% of patients develop hepatocellular carcinoma [37]. The evidence demonstrating the association of chronic HCV infection with the development of cirrhosis and hepatocellular carcinoma reinforces the need to identify the disease early and treat patients at risk of complications related to the virus, in order to reduce the morbidity and mortality of hepatitis C.

18.5.5 Kidney Involvement

Chronic HCV infection can be analyzed as a systemic disease, with involvement of organs other than the liver. Patients with chronic HCV infection have an increased risk of developing nonhepatic complications, which are reported in more than 2/3 of these patients. Autoimmune manifestations, lymphoproliferative diseases, cardiovascular, renal, metabolic, and central nervous system diseases are some of the extrahepatic alterations widely described in the literature.

HCV infection is associated with kidney disease more frequently than HBV infection. Nephropathy associated with HCV infection may be asymptomatic, manifesting only with changes in urinary sediment. However, it may progress to severe loss of kidney function and the need for dialysis. Routine urine testing is recommended in all patients with HCV infection to screen for proteinuria and hematuria, given the high frequency of kidney disease in this group of patients [19].

Glomerulopathies stand out as an associated condition in patients with chronic HCV infection. Membranoproliferative glomerulonephritis type I associated with mixed cryoglobulinemia is the most common form of associated kidney disease. They are characterized by diffuse accentuation of the glomerular tuft, with extensive expansion of the mesangial matrix, hypercellularity with mesangial predominance, thickening of capillary loops, and duplication of the basement membrane. Immunofluorescence shows diffuse or segmental deposition of IgG, IgM, kappa, lambda, and complement components along the capillary loops. Electron microscopy shows electron-dense immune complexes in subendothelial and mesangial areas [18, 19].

Less frequently, membranoproliferative glomerulonephritis without cryoglobulinemia, membranous glomerulopathy, and mesangial proliferative glomerulonephritis have been described. Occasional cases of focal segmental glomerulosclerosis, fibrillary and immunotactoid glomerulopathy, and thrombotic microangiopathy have been reported [18]. The kidney histopathological findings associated with HCV infection [38] can be seen in Figure 18.2.

As with hepatitis B, the most common clinical presentation of HCV-associated kidney disease is nephrotic syndrome, although in this case, it is usually associated with a nephritic component and loss of kidney function. In cases associated with cryoglobulinemia, systemic manifestations (purpura, nodules, ulcers, paresthesias, arthralgias, asthenia) are also observed [18]. The most common clinical and histological presentation (70–80%) in mixed cryoglobulinemia-HCV is acute or chronic membranoproliferative glomerulonephritis with endothelial deposits. In the urinalysis, the most common presentation (55%) is proteinuria with microscopic hematuria. Acute nephrotic syndrome (20%) or nephritic syndrome (25%) may also be an expression of kidney

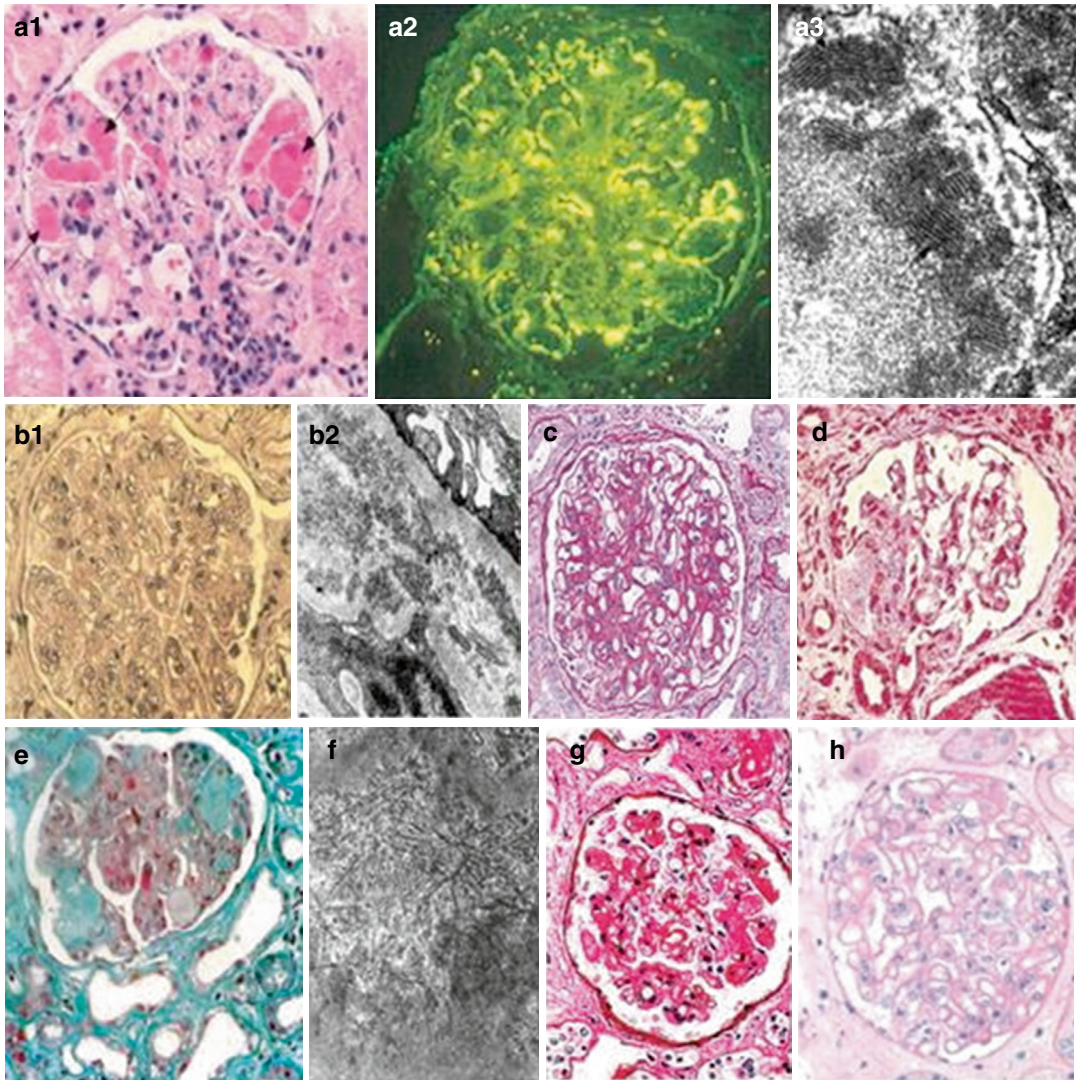


Fig. 18.2 Renal histopathologic findings associated with hepatitis C. (**a**) Cryoglobulinemic membranoproliferative glomerulonephritis; (A1) H&E stain showing mesangial proliferation and matrix expansion with capillary thrombi (arrows); (A2) immunofluorescence showing subendothelial IgM deposits; (A3) electron microscopy showing the typical fingerprint appearance of cryoglobulin deposits. (**b**) Noncryoglobulinemic membranoproliferative glomerulonephritis; (B1) methenamine silver stain showing subendothelial interposition of mesangial matrix with a typical tram-track appearance; (B2) electron microscopy showing subendothelial aggregates of virus-like particles. (**c**) Membranous nephropathy; PAS stain showing thickening of the basement membrane; note the mesangial sclerotic changes and mild mesangial hyperplasia. (**d**) Focal and segmental sclerosis; H&E stain showing shrinkage of the glomerulus with a sclerotic segment. (**e**) Amyloidosis; Masson's trichrome stain showing mesangial proliferation, matrix expansion, amyloid deposits (confirmed by Congo red stain), and capillary thrombi associated with cryoglobulinemia. (**f**) Fibrillary glomerulonephritis. Electron microscopy showing the typical 18–22 nm fibers. (**g**) Posttransplant thrombotic microangiopathy, H&E stain. (**h**) Transplant glomerulopathy; H&E stain showing swelling and endothelial cell proliferation. (©2008 European Renal Association. Reprinted with permission from Barsou et al. [38])

involvement in cryoglobulinemia. New-onset arterial hypertension is seen in 80% of cases. The acute-phase complement component (C1q, C4) is very low in this condition. Chronic kidney disease may be evident in 10–20% of patients with HCV-cryoglobulinemia after a decade of follow-up, and it is estimated that patients with hepatitis C who receive treatment have a 30% reduction in the risk of developing kidney disease.

Several authors have found evidence of an association between HCV infection and other glomerular diseases in both native and transplanted kidneys [39, 40]. A large case-control study conducted among retired US military men hospitalized between 1992 and 1999 identified 34,204 patients who were hospitalized with HCV (cases) and 136,816 randomly selected individuals without HCV (controls) [41]. There was a higher proportion of membranoproliferative glomerulonephritis among patients with HCV (0.36% vs. 0.5%, $p < 0.1$), but not of membranous glomerulopathy (0.33% vs. 0.19%, $p = 0.86$). HCV infection was associated with a 40% higher prevalence of kidney injury (serum creatinine ≥ 1.5 mg) compared with the population without HCV infection, even after adjusting for age, sex, race, diabetes, and hypertension [42] Some surveys extracted from large clinical databases have suggested an impact of HCV on the prevalence and incidence of kidney disease in the general population [42–46]. HCV and HIV coinfection has also been associated with a significantly increased risk of kidney disease [46, 47]. Another more recent review suggested that HCV affects kidney function in the general population [39]. In multivariate analysis, positive anti-HCV status was associated with low glomerular filtration rate (odds ratio up to 2.80). A significant association between HCV and proteinuria has been reported in apparently healthy individuals (odds ratio 1.14–1.99) [43–50]. Anti-HCV positivity was significantly associated with proteinuria, independently of common metabolic factors such as diabetes mellitus, arterial hypertension, obesity, and dyslipidemia.

The *Kidney Disease Improving Global Outcomes* (KDIGO) recommends that all patients with chronic kidney disease be tested for HCV [51]. Serum ribavirin levels should be measured regularly due to the risk of anemia. Ribavirin should be avoided in the treatment of patients with chronic kidney disease.

The possibility of eradicating hepatitis C with the advent of new antiviral drugs recently made available points to the prospect of a lesser future impact of this disease and its hepatic and non-hepatic consequences, including kidney disease.

The pathophysiology of hepatitis C-associated nephropathy includes immune-mediated injury and direct cytotoxic effects of the virus. Other factors, including genetic characteristics and manifestations associated with the viral infection itself (decompensated cirrhosis, cryoglobulinemic vasculitis, and comorbidities such as diabetes), also play an important role in the genesis of kidney injury. The deposition of immune complexes (cryoprecipitates and non-cryoprecipitates) containing HCV antigens in kidney tissue is the main pathogenetic mechanism of hepatitis C-associated glomerulonephritis [52].

Patients with decompensated cirrhosis may develop acute kidney injury (hepatorenal syndrome), which is one of the consequences of splanchnic vasodilation due to portal hypertension, which leads to kidney hypoperfusion [52].

Histopathological findings in HCV-associated nephropathy include the following: mesangial proliferation and deposits of immune complexes, including HCV particles (membranoproliferative glomerulonephritis); mesangial matrix expansion and mesangial cell proliferation (mesangial proliferative glomerulonephritis); interstitial fibrosis and leukocyte infiltrate, usually focal (tubulointerstitial nephritis); IgA deposits (IgA nephropathy); arterioles with intimal thickening, edema, narrowing in the glomerular capillary lumen, and thrombi (thrombotic microangiopathy); glomerular atrophy and sclerosis; podocyte deletion (focal and segmental glomerulosclerosis); and extracellular deposits of microfibrils in the mesangium and glomerular capillary walls (immunotactoid and fibrillary glomerulopathy) [52].

18.5.6 Treatment

According to the most recent clinical protocol of the Ministry of Health for the treatment of HCV infection, the main objective of treatment is the eradication of the virus. In addition, the current treatment of hepatitis C also aims to increase the patient's life expectancy and quality of life, reduce the incidence of complications of chronic liver disease, and reduce the transmission of the virus [1, 34]. Specific treatment with antivirals is indicated for [1] patients not previously treated with daclatasvir, simeprevir, sofosbuvir, and the combination of the drugs ombitasvir hydrate, veruprevir dihydrate/ritonavir, and dasabuvir sodium monohydrate (3D) and [2] who present the following test results: (a) METAVIR F3 or F4 (advanced liver fibrosis) or clinical evidence of cirrhosis and (b) liver biopsy or liver elastography with METAVIR F2 result present for more than 3 years.

In the absence of advanced liver disease, treatment of hepatitis C is indicated for patients diagnosed with chronic hepatitis C included in the following situations: coinfection with HIV; coinfection with HBV; extrahepatic manifestations with disabling motor neurological involvement, cutaneous porphyria, severe lichen planus with mucosal involvement; cryoglobulinemia with target organ manifestation (glomerulonephritis, vasculitis, involvement of the eyes, lungs, and peripheral and central nervous system); polyarteritis nodosa; chronic kidney disease; Idiopathic thrombocytopenic purpura (ITP); post-liver and other solid organ transplantation; lymphoma, monoclonal gammopathy, multiple myeloma, and other malignant hematologic diseases; autoimmune hepatitis; hemophilia and other hereditary coagulopathies; hemoglobinopathies, and hemolytic anemias [1, 34].

Patients who do not fit into the situations presented should be monitored periodically until an indication for therapy is established. Patients coinfected with HIV/HCV genotype 1 will only be eligible for treatment with the combination of the drugs ombitasvir, veruprevir/ritonavir, and dasabuvir (3D), when they have advanced kidney disease (GFR $\leq$ 30mL/min) and have their ARV regimen adjusted in order to avoid unwanted drug interactions [1, 34].

Transplant patients other than liver transplants, including kidney transplant patients, should be treated in the same way as patients with recurrence after liver transplantation, according to genotype. To date, there is no evidence to determine differentiated treatment for these patients. The safety of new drugs for the treatment of solid organ transplant patients has not been fully elucidated. It is recommended that these patients be monitored by specialists, following the respective Clinical Protocols and Therapeutic Guidelines [1, 34].

The treatment of HCV-associated glomerulonephritis is similar to that of glomerular diseases in general, with antiproteinuric drugs (ACEI or ARB), blood pressure control, dyslipidemia, and other general supportive measures. Specific antiviral treatment recommended for HCV infection generally contributes to remission of glomerular disease and should be recommended according to current guidelines, according to the viral genotype [18].

18.6 Hepatitis E

18.6.1 The Virus (VHE)

HEV belongs to the *Hepeviridae family*, whose viruses that infect humans are classified into four genotypes (HEV 1–4) and which replicate primarily in hepatocytes [5].

18.6.2 Epidemiology

HEV has been responsible for major epidemics in adults in Asia, the Middle East, and North Africa [5]. It is estimated that approximately 20 million cases of hepatitis E occur annually worldwide, of which 3.3 million are symptomatic [53]. There are no significant prevalence data on hepatitis E in Brazil.

18.6.3 Natural History

The characteristics of hepatitis E are typical of acute hepatitis, with an incubation period ranging from 15 to 50 days. The infection is mediated by the host's immune response, making it possible to eliminate the virus and acquire specific immunity [5]. The infection occurs via the fecal-oral route. After reaching the liver, the virus begins the process of liver damage. Hepatitis E rarely becomes chronic and generally has a favorable evolution [5].

18.6.4 Clinical Manifestations

The disease begins with a pre-icteric phase, with gastrointestinal symptoms of epigastric pain, nausea, and vomiting. There may also be fever and arthralgias. The acute form is self-limiting. Extrahepatic manifestations have been described, including neurological and kidney injuries [5].

18.6.5 Kidney Involvement

The spectrum of kidney manifestations associated with hepatitis E includes ARF, glomerulopathies, and tubular and interstitial lesions [54]. Kidney involvement in hepatitis E usually has a benign course and is self-limited. ARF has been described in recipients of solid organs infected with HEV [5]. Glomerulopathies associated with HEV infection are frequently found in transplant patients and immunocompromised individuals [54] , and membranoproliferative and membranous glomerulonephritis are well documented and may also occur in immunocompetent individuals [5, 55, 56]. Complete remission of kidney injury has been described after acute hepatitis E [56].

18.6.6 Treatment

Immunocompetent patients with hepatitis E generally have a favorable evolution, spontaneously eliminating the virus, and do not require specific treatment [5]. There is no specific treatment for hepatitis E. There are studies with ribavirin for the treatment of hepatitis E, but it cannot yet be indicated because there is insufficient evidence [5, 57].

Table 18.1 summarizes kidney involvement in viral hepatitis.

Table 18.1 Viral hepatitis and characteristics of kidney involvement

Virus	Renal manifestations	Histopathological findings
Hepatitis A	AKI	NTA, NIA
Hepatitis B	Glomerulonephritis, nephrotoxicity, tubular injury	Membranoproliferative GN membranous GN
Hepatitis D	No cases recorded	–
Hepatitis C	Glomerulonephritis, nephrotic syndrome, DRC	Membranoproliferative GN, mixed cryoglobulinemia, membranous GN, mesangial proliferative GN, GESF, fibrillar and immunotactoid glomerulopathy, thrombotic microangiopathy
Hepatitis E	AKI glomerulonephritis	Membranoproliferative GN membranous GN

AKI acute kidney injury, *AT* acute tubular necrosis, *AIN* acute interstitial nephritis, *GN* glomerulonephritis, *FSGS* focal segmental glomerulosclerosis, *CKD* chronic kidney disease

18.7 Conclusion

Viral hepatitis is a major public health problem, affecting millions of people worldwide. Glomerulonephritis is the most common kidney complication, and specific treatment of hepatitis is usually beneficial for improving kidney disease. Early diagnosis of hepatitis and, consequently, of potential complications, including kidney dysfunction, is of utmost importance to ensure the best possible outcome for this group of patients.

References

1. Brazil, Ministry of Health. Secretariat of Health Surveillance. Department of Surveillance, Prevention and Control of Sexually Transmitted Infections, HIV/AIDS and Viral Hepatitis. Technical Manual for the Diagnosis of Viral Hepatitis. 2nd ed. Brasília: Ministry of Health; 2018.
2. Abutaleb A, Kottilil S. Hepatitis A: epidemiology, natural history, unusual clinical manifestations, and prevention. Gastroenterol Clin North Am. 2020;49(2):191–9. https://doi.org/10.1016/j.gtc.2020.01.002.
3. Odenwald MA, Paul S. Viral hepatitis: Past, present, and future. World J Gastroenterol. 2022;28:1405–29.
4. Castaneda D, Gonzalez AJ, Alomari M, Tandon K, Zervos XB. From hepatitis A to E: a critical review of viral hepatitis. World J Gastroenterol. 2021;27:1691–715.
5. Veronesi R. Treatise on infectology. 6th ed. Rio de Janeiro: Atheneu; 2021.
6. Kim SH, Yoon HE, Kim YK, Kim JY, Choi BS, Choi YJ, et al. Acute hepatitis A-associated acute renal failure in adults. Nephron Clin Pract. 2008;109:c127–32.
7. Park JY, Gwak GY, Kim JM, Oh HJ, Yi NJ, Suh KS, et al. Renal outcomes after liver transplantation in fulminant hepatitis A with acute kidney injury: comparison with hepatorenal syndrome. Transplant Proc. 2015;47:709–17.
8. Claude-Del Granado R, Espinosa-Cuevas M. Herbal nephropathy. Contrib Nephrol. 2021;199:143–54.
9. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2007;45:507–39.
10. Trépo C, Chan HLY, Lok A. Hepatitis B virus infection. Lancet. 2014;384:2053–63.
11. Sunbul M. Hepatitis B virus genotypes: global distribution and clinical importance. World J Gastroenterol. 2014;20:5427–34.
12. Seeger C, Mason WS. Molecular biology of hepatitis B virus infection. Virology. 2015;479–480:672–86.
13. Tong S, Revill P. Overview of hepatitis B viral replication and genetic variability. J Hepatol. 2016;64:S4–S16.
14. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimates of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386:1546–55.
15. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30:2212–9.
16. Souto FJD. Distribution of hepatitis B infection in Brazil: the epidemiological situation at the beginning of the 21st century. Rev Soc Bras Med Trop. 2015;49:11–23.
17. Ondenwald MA, Paul S. Viral hepatitis: past, present, and future. World J Gastroenterol. 2022;28:1405–29.
18. Valente LM, Melo SMO. Glomerulopathies associated with viral hepatitis. In: Moura LRR, Alves MAR, Santos DR, Pecoits-Filho R, editors. Textbook of nephrology. 1st ed. Rio de Janeiro: Atheneu; 2018. p. 775–82.
19. Narciso HR, Schiavon JLN, Schiavon LL, Narciso RC. Viral hepatitis and chronic kidney disease. In: Riella MC, editor. Principles of nephrology and hydroelectrolytic disorders. 6th ed. Rio de Janeiro: Guanabara-Koogan; 2018. p. 801–14.
20. Chan MT. Hepatitis B and renal disease. Curr Hepatitis Rep. 2010;9:99–105.
21. Deray G, Buti M, Gane E, Jia JD, Chan HLY, Craxi A, Piratvisuth T, Pol S. Hepatitis B virus infection and the kidney: renal abnormalities in HBV patients, antiviral drugs handling, and specific follow-up. Adv Hepatol. 2015;2015:596829.
22. Shah AS, Amarapurkar DN. Spectrum of hepatitis B and renal involvement. Liver Int. 2018;38:23–32.
23. Manns MP, Maasoumy B. Breakthroughs in hepatitis C research: from discovery to cure. Nat Rev Gastroenterol Hepatol. 2021;19:533–50.
24. Borgia SM, Hadskog C, Parhy B, Hyland RH, Stamm LM, Brainard DM, et al. Identification of a novel hepatitis C virus genotype from Punjab, India: expanding classification of hepatitis C virus into 8. J Infect Dis. 2018;218:1722–9.
25. Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: an up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016;22:7824–40.
26. Beyrer C, Sripaipan T, Tovanabutra S, et al. High HIV, hepatitis C and sexual risks among drug-using men who have sex with men in northern Thailand. AIDS. 2005;19:1535–40.
27. Ishi K, Suzuku F, Saito A, Yoshimoto S, Kubota T. Prevalence of human immunodeficiency virus, hepatitis B and hepatitis C virus antibodies and hepatitis B antigen among commercial sex workers in Japan. Infect Dis Obstet Gynecol. 2001;9:215–9.

28. Kweon SS, Shin MH, Song HJ, Jeon DY, Choi JS. Seroprevalence and risk factors for hepatitis C virus infection among female commercial sex workers in South Korea who are not intravenous drug users. Am J Trop Med Hyg. 2006;74:1117–21.
29. Paltanin LF, Reiche EMV. Seroprevalence of hepatitis C antibodies in blood donors. Brazil. Rev Saúde Pública. 2002;36:393–9.
30. Pereira LMMB, Martelli CM, Moreira RC, Merchan-Hamman E, Stein AT, Cardoso MR, et al. Prevalence and risk factors of hepatitis C virus infection in Brazil, 2005 through 2009: a cross-sectional study. BMC Infect Dis. 2013;13:60.
31. Thimme R, Oldach D, Chang KM, Steiger C, Ray SC, Chisari FV. Determinants of viral clearance and persistence during acute hepatitis C virus infection. J Exp Med. 2001;194:1395–406.
32. Villano AS, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology. 1999;29:908–14.
33. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62:932–54.
34. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. J Hepat. 2017;66:153–94.
35. World Health Organization. Guidelines for the Screening Care and Treatment of Persons with Chronic Hepatitis C Infection. Geneva, 2016. Available at: https://www.ncbi.nlm.nih.gov/books/NBK493344/. Accessed on 21 May 2018.
36. Seeff LB. Natural history of chronic hepatitis C. Hepatology. 2002;36:S35–46.
37. Charlton M, Hepatitis C. Infection in liver transplantation. Am J Transplant. 2001;8:197–203.
38. Barsoum RS. Hepatitis C virus: from entry to renal injury—facts and potentials. Nephrol Dial Transplant 2007; 22: 1840-1848.
39. Fabrizi F, Poordad FF, Martin P. Hepatitis C infection and the patient with end-stage renal disease. Hepatology. 2002;36:3–10.
40. Roth D, Cirocco R, Zucker K, et al. De novo membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. Transplantation. 1995;59:1676–82.
41. El-Serag HB, Hampel H, Yeh C, et al. Extrahepatic manifestations of hepatitis C among United States male veterans. Hepatology. 2002;36:1439–45.
42. Dalrymple LS, Koepsell T, Sampson J, et al. Hepatitis C virus infection and the prevalence of renal insufficiency. Clin J Am Soc Nephrol. 2007;2:715–21.
43. Butt AA, Wang X, Fried LF. HCV infection and the incidence of CKD. Am J Kidney Dis. 2011;57:396–402.
44. Lee JJ, Lin MY, Yang YH, et al. Association of hepatitis C and B virus infection with CKD in an endemic area in Taiwan: a cross-sectional study. Am J Kidney Dis. 2010;56:23–31.
45. Tsui JI, Vittinghoff E, Shlipak MG, et al. Relationship between hepatitis C and chronic kidney disease: results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol. 2006;17:1168–74.
46. Izzedine H, Sene D, Cacoub P, et al. Kidney diseases in HIV/HCV-co-infected patients. AIDS. 2009;23:1219–26.
47. Wyatt CM, Malvestutto C, Coca SG, et al. The impact of hepatitis C virus coinfection on HIV-related kidney disease: a systematic review and meta-analysis. AIDS. 2008;22:1799–807.
48. Fabrizi F, Plaisier E, Saadoun D, et al. Hepatitis C virus infection, mixed cryoglobulinemia, and kidney disease. Am J Kidney Dis. 2013;61:623–37.
49. Huang JF, Chuang WL, Dai CY, et al. Viral hepatitis and proteinuria in an area endemic for hepatitis B and C infections: another chain of link? J Intern Med. 2006;260:255–62.
50. Liangpunsakul S, Chalasani N. Relationship between hepatitis C and microalbuminuria: results from the NHANES III. Kidney Int. 2005;67:285–90.
51. Kidney Disease: Improving Global Outcomes (KDIGO) Hepatitis C Working Group. KDIGO. Clinical Practice Guideline FOR the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. Kidney Int. 2022;2022(102):S129–205.
52. Ferri C, Giuggioli D, Colaci M. Renal manifestations of hepatitis C Virus. Clin Liver Dis. 2017;21:487–97.
53. Brazil, Ministry of Health. Hepatitis E. https://www.gov.br/aids/pt-br/assuntos/hepatites-virais/hepatite-e. Updated on 04/26/2022
54. Kovvuru K, Carbajal N, Pakanati AR, Thongprayoon C, Hansrivijit P, Boonpheng B, Pattharanitima P, NIssaisorarakarn V, Cheugpasitporn W, Kanduri SR. Renal manifestations of hepatitis E among immunocompetent and solid organ transplant recipients. World J Hepatol. 2022;14:516–24.
55. Guinault D, Ribes D, Delas A, Milongo D, Abravanel F, Puissant-Lubrano B, Izopet J, Kamar N. Hepatitis E virus-induced cryoglobulinemic glomerulonephritis in a nonimmunocompromised person. Am J Kidney Dis. 2016;67:660–3.
56. Takanohashi S, Sugiura T, Koyano A, Ueno T, Rachi H, Shiratori K, Shimasaki M, Igarashi H, Kitayama Y, Togawa A. Complete remission of primary membranous nephropathy following hepatitis E infection. CEN Case Rep. 2023;12:384–9.
57. Iqbal H, Mehmood BF, Sohal A, Roytman M. Hepatitis E infection: a review. World J Virol. 2023;12:262–71.

19 Nephropathy Due to Influenza A (H1N1) Infection

Edgar Sanclemente-Paz

19.1 Epidemiology and Clinical Features

Influenza A is a viral infection associated with significant morbidity and mortality. The most common complications occur in children under 1 year of age and people over 65 years of age, especially if there are preexisting factors such as chronic lung disease, obesity, and diabetes. Its main manifestation is pneumonia caused by the virus, which produces acute lung injury, which requires mechanical ventilation in most cases [1, 2].

The inflammatory phenomenon triggered by the virus leads some patients to develop multiorgan damage, in addition to a direct action of the virus on the affected organs [3].

19.2 Nephrotoxicity

Kidney complications during the course of influenza A (H1N1) virus infection are relatively frequent and may contribute to the deterioration of the critically ill patient. These pathological conditions include: acute kidney injury (AKI) with tubular necrosis, hemolytic uremic syndrome, disseminated intravascular coagulation, acute glomerulonephritis, Goodpasture syndrome, and acute tubulointerstitial nephritis [4–8].

AKI is a common occurrence in this viral infection, and its etiopathogenesis includes renal hypoperfusion and vasoconstriction of the kidney vessels during systemic vasodilation of the shock state, resulting in acute tubular necrosis. Other factors involved in this pathological condition are rhabdomyolysis and hemolysis [9–16].

The incidence of AKI during the course of influenza A (H1N1) virus infection varies between 18% and 62% of patients, in some cases associated with rhabdomyolysis due to a toxic effect of the virus on muscle fibers and the action of proinflammatory cytokines. It occurs mainly in children, although more and more cases are observed in adults with significant elevation of creatine kinase [17–29].

E. Sanclemente-Paz (✉)
Department of Internal Medicine,
Faculty of Medicine, University of Cauca,
Popayán, Cauca, Colombia
e-mail: esanclemente@imbanaco.com.co

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_19

19.3 Treatment and Outcome

Mortality is between 16% and 30%, mainly in patients who required dialysis; however, in patients who survived, a complete recovery of their renal function was observed. Excessive hydration is a risk factor for the appearance of acute kidney injury and mortality in cases of infection with the H1N1 20-44 virus (Fig. 19.1).

A possible association between influenza vaccination and the risk of chronic kidney disease in hypertensive patients is described [30–39].

Cases of acute glomerulonephritis with hypocomplementemia, mesangial proliferative glomerulonephritis, granulomatous interstitial nephritis, and acute tubulointerstitial nephritis are described, which may eventually cause acute kidney injury (AKI) that may eventually require renal replacement therapy [30] (Fig. 19.2).

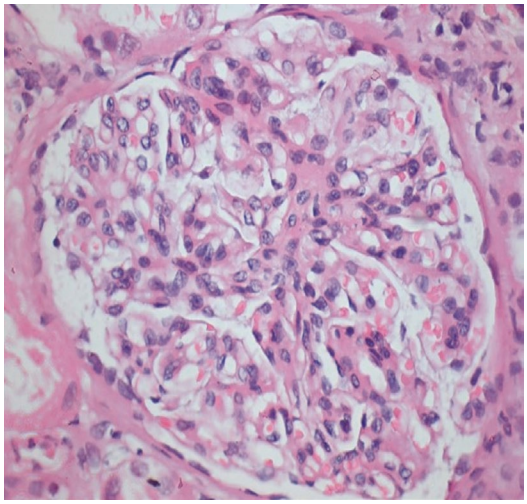


Fig. 19.2 Kidney injury associated with influenza (H1N1). Tubular necrosis; mesangial proliferation. (Reproduced with permission from Nigan et al. [37])

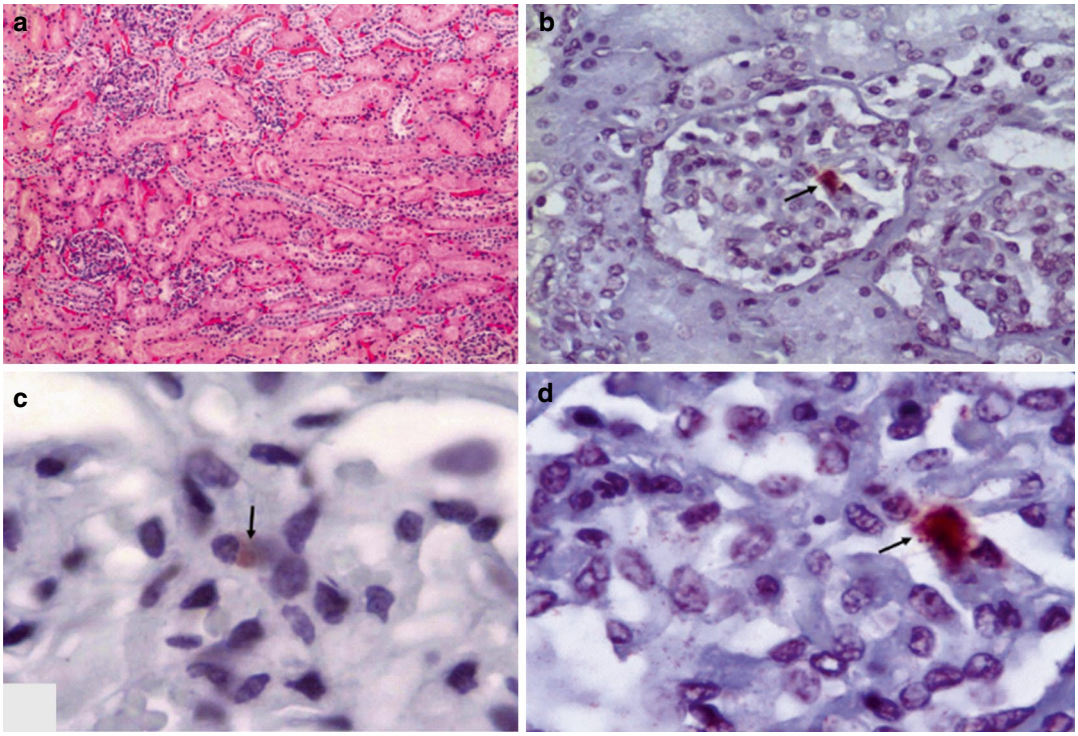


Fig. 19.1 Kidney injury associated with influenza (H1N1). Viral antigen in the glomerulus. (Reproduced with permission from Carmona et al. [5])

19.4 Take-Home Message

- Precautions should be taken to avoid the spread of this viral disease.
- Children, the elderly, and people with comorbidities are more susceptible to serious complications.
- Seek medical attention in time when symptoms are severe.

References

1. Rothberg MB, Haessler SD. Complications of seasonal and pandemic Influenza. Crit Care Med. 2010;38:e91–7.
2. Thorner AR. Epidemiology of pandemic H1N1 influenza ('swine influenza'). UpToDate; 2017.
3. Bautista E, Arcos M, Jimenez-Alvarez L, et al. Angiogenic and inflammatory markers in acute respiratory distress syndrome and renal injury associated to A/H1N1 virus infection. Exp Mol Pathol. 2013;94:486–92.
4. Printza N, Roilides E, Kotsiou M, et al. Pandemic influenza A (H1N1) 2009-associated hemolytic uremic syndrome. Pediatr Nephrol. 2011;26:143–4.
5. Carmona F, Carlotti APCP, Ramalho LNZ, et al. Evidence of renal infection in fatal cases of 2009 pandemic Influenza A (H1N1). Am J Clin Pathol. 2011;136:416–23.
6. Watanabe T. Renal complications of seasonal and pandemic Influenza A virus infections. Eur J Pediatr. 2013;172:15–22.
7. Yang Y, Tang H. Aberrant coagulation causes a hyperinflammatory response in severe influenza pneumonia. Cell Mol Immunol. 2016;13:432–42.
8. Mohammad KN, Chan EYY, Lau SY-F, et al. Relationship between acute kidney injury, seasonal influenza, and environmental factors: a 14-year retrospective analysis. Environ Int. 2021;153:106521.
9. Trimarchi H, Greloni G, Campolo-Girard V, et al. H1N1 infection and the kidney in critically ill patients. J Nephrol. 2010;23:725–31.
10. Sato E, Nakamura T, Koide H. Rhabdomyolysis induced by Influenza A infection: Case report and review of literature. Ther Apher Dial. 2011;15:208–9.
11. Nin N, Lorente JA, Sánchez-Rodríguez C, et al. Kidney histopathological findings in fatal pandemic 2009 Influenza A (H1N1). Intensive Care Med. 2011;37:880–1.
12. Wiwanitkit V. Rhabdomyolysis in influenza A/H1N1. Wien Klin Wochenschr. 2014;126:140.
13. Dalbhi SA, Alshahrani HA, Almadi A, et al. Prevalence and mortality due to acute kidney injuries in patients with influenza A (H1N1) viral infection: a systemic narrative review. Int J Health Sci (Qassim). 2019;13:56–62.
14. Dolipska J, Krzanowski M, Krzanowska K, Kuźniewski M. Acute kidney injury caused by rhabdomiolysis secondary to Influenza (AH1N1) infection. Przegląd Lekarski; 2019.
15. Askari MK, Shabpiray H, Deering C. A case of influenza H1 2009 with severe rhabdomyolysis and secondary acute renal failure with liver involvement. Contagion; 2020.
16. Huangfu Y, Wang J, Feng J, Zhang Z-L. Distal renal tubular system-on-a-chip for studying the pathogenesis of Influenza A virus-induced kidney injury. Lab Chip. 2023;23:4255–64.
17. Runnstrom M, Ebied AM, Khoury AP, Reddy R. Influenza-induced rhabdomyolysis. BMJ Case Rep. 2018;11:e226610.
18. Wu K-H, Lai HC. Rhabdomyolysis following influenza A infection in children: Case report and literature review. Int J Clin Exp Med. 2020;13:10039–44.
19. Rocano Once IP. Rabdomiólisis asociado a infección por virus de la Influenza: Reporte de caso. Tesis Pregrado Medicina. Cuenca: Universidad Católica de Cuenca; 2023.
20. Sood MM, Rigatto C, Zarychanski R, et al. Acute kidney injury in critically ill patients infected with 2009 pandemic influenza A(H1N1): Report from a Canadian province. Am J Kidney Dis. 2010;55:848–55.
21. Abdulkader RCRM, Ho YL, de Sousa SS, et al. Characteristics of acute kidney injury in patients infected with the 2009 influenza A (H1N1) virus. Clin J Am Soc Nephrol. 2010;5:1916–21.
22. Lai C-C, Wang C-Y, Lin H-I. Rhabdomyolysis and acute kidney injury associated with 2009 pandemic Influenza A(H1N1). Am J Kidney Dis. 2010;55:615.
23. Parikh M, Dolson G, Ramanathan V, Sangsiraprapha W. Novel H1N1-associated rhabdomyolysis leading to acute renal failure. Clin Microbiol Infect. 2010;16:330–2.
24. Jung JY, Park BH, Hong S-B, et al. Acute kidney injury in critically ill patients with pandemic Influenza A pneumonia 2009 in Korea: a multicenter study. J Crit Care. 2011;26:577–85.
25. Demirjian SG, Raina R, Bhimraj A, et al. 2009 influenza A infection and acute kidney injury: incidence, risk factors, and complications. Am J Nephrol. 2011;34:1–8.
26. Unverdi S, Akay H, Ceri M, et al. Acute kidney injury due to rhabdomyolysis in H1N1 Influenza infection. Ren Fail. 2011;33:450–1.
27. Bagshaw SM, Sood MM, Canadian Critical Care Trials Group H1N1 Collaborative, et al. Acute kidney injury among critically ill patients with pandemic H1N1 influenza A in Canada: cohort study. BMC Nephrol. 2013;14:123.
28. Romão Junior JE. Acute kidney injury in patients with the Influenza A virus (H1N1). Jornal Brasileiro de Nefrologia. 2013;
29. Tignanelli CJ, Wiktor AJ, Vatsaas CJ, et al. Outcomes of acute kidney injury in patients with severe ARDS due to Influenza A(H1N1) pdm09 Virus. Am J Crit Care. 2018;27:67–73.

30. Hao W-R, Yang T-L, Lai Y-H, et al. The association between influenza vaccine and risk of Chronic Kidney Disease/Dialysis in patients with Hypertension. Vaccines (Basel). 2023;11:1098.
31. Kupferman JC, Trachtman H, Spitzer ED. Acute glomerulonephritis and acute kidney injury associated with 2009 Influenza A: H1N1 in an infant. Pediatr Nephrol. 2011;26:153–4.
32. Jain T, Hemington L, Etuwewe B. A case of post-infectious glomerulonephritis following infection with influenza A subtype H1N1. Pediatr Nephrol. 2011;26:151–2.
33. Ashtiani N, Mulder MF, van Wijk JAE, Bokenkamp A. A case of tubulointerstitial nephritis in a patient with an influenza H1N1 infection. Pediatr Nephrol. 2012;27:1985–7.
34. Sturdivant RL, Self S, Bilic M. Membranoproliferative glomerulonephritis associated with Influenza A infection. Am J Med Sci. 2012;344:234–6.
35. Sevignani G, Soares MF, Marques GL, et al. Acute kidney injury in patients infected by H1N1: Clinical histological correlation in a series of cases. Jornal Brasileiro de Nefrologia. 2013;35:185–90.
36. Kute VB, Vanikar AV, Shah PR, et al. Mesangial proliferative glomerulonephritis with acute tubule interstitial nephritis leading to acute kidney injury in influenza A (H1N1) infection. Indian J Nephrol. 2014;24:114–6.
37. Nigam Lovelesh SC, Vanikar A, Patel R, Trivedi H. Spectrum of histopathological findings in patients with acute kidney injury following H1N1 influenza infection: a study of three cases. Ann Trop Med Public Health. 2015;8:296.
38. Milosevski-Lomić G, Marković-Lipkovski J, Kostić M, et al. Granulomatous interstitial nephritis associated with influenza A H1N1 infection: a case report. Srp Arh Celok Lek. 2016;144:215–8.
39. Aceituno D, Fica A, Fasce R, et al. Glomerulonefritis aguda con requerimiento de diálisis asociada a influenza A H1N1pdm09: Comunicación de dos casos. Rev chil infectol. 2017;34:81–6.

Part V

Kidney Diseases Associated with Parasitic Agents

20 Kidney Involvement in Chagas' Disease (American Trypanosomiasis)

Elizabeth De Francesco Daher, Geraldo Bezerra da Silva Junior, Elvino Barros, João Filipe Cavalcante Uchoa Furtado, Pedro Vianna Caldas Ribeiro, Verônica Verleine Hörbe Antunes, Gabriela Vieira Steckert, Gabriel Sartori Pacini, and Renata Asnis Schuchmann

20.1 Introduction

Chagas disease or American trypanosomiasis is caused by the flagellated protozoan *Trypanosoma cruzi*, and its vectors are insects of the *Triatomidae* family, *Triatoma infestans*, *Rhodnius prolixus*, and *Panstrongylus megistus* (an insect popularly known as the "kissing bug" or "cone-nosed bug") [1–3].

Transmission occurs from the contact of *T. cruzi* with blood, through the feces of the "kissing bug," with the injured skin or mucosa of the eyes. Transmission can also occur by oral ingestion of the parasites, by inoculation, through the wound caused by insect bites or mucous membranes, fecal material containing the parasite, and also by vertical transmission, through blood transfusion or transplantation of organs from infected donors [3–8]. Moreover, the disease can be diagnosed in neonates born to women with Chagas disease [6]. The complications of Chagas disease are mainly related to the gastrointestinal tract (megacolon and megaesophagus) and heart disease. Kidney involvement is rarely described [9].

20.2 Epidemiology

Chagas disease is a common tropical disease in low- and middle-income countries, first described in 1909 by Brazilian researcher Carlos Chagas, being endemic in almost all Latin American countries [10]. The World Health Organization (WHO) estimates that 6–7 million individuals are infected worldwide, mostly in Latin America. Recent esti-

E. De Francesco Daher
Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

G. Bezerra da Silva Junior (✉) · J. F. C. U. Furtado · P. V. C. Ribeiro
School of Medicine, University of Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

E. Barros
School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil

V. V. H. Antunes
Division of Nephrology, Hospital de Clinicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil
e-mail: vantunes@hcpa.edu.br

G. V. Steckert · G. S. Pacini· R. A. Schuchmann
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brasil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_20

mates in 21 Latin American countries, based on 2010 data, indicated 5.7 million individuals infected with *T. cruzi* (1.5 million in Argentina, 1.2 million in Brazil, 0.8 million in Mexico, and 0.6 million in Bolivia). Since 1975, a nationwide program for the control of vector transmission of the disease in Brazil has been systematized, with indicators pointing to a virtual elimination of the main vector species involved in the disease transmission in the country, the *Triatoma infestans*, with some foci still persisting in the northeast of Goiás and south of Tocantins states, in São Francisco region, in the state of Bahia, in the north of Rio Grande do Sul state and in the south- east of Piauí state [3, 10–12]. Currently, the epidemiological profile of the disease in Brazil is characterized by a new scenario—predominance of chronic cases from past acquired infections and outbreaks of acute Chagas disease related to the ingestion of contaminated food (mainly acai berry and sugar cane juice) and some isolated cases by extra-domiciliary vector transmission in the Amazon region [4, 13, 14].

The number of Chagas disease cases has decreased significantly in recent years, from 30 million cases in the 1990s to 5.7 million in 2010, with an annual incidence dropping from 700,000 to 29,900, and a number of deaths decreasing from 45,000 to 12,000 [3, 15].

20.3 Pathophysiology

Chagas disease lesions are due to inflammatory response, cell damage, and parasite-induced fibrosis. Such alterations are usually intense in the acute phase, with several cycles of intracellular parasite multiplication, and less marked in the chronic phase, in which infection is partially controlled by the immune response [3, 6, 16, 17].

Chagas disease is characterized by the involvement of the parasympathetic nervous system and, to a lesser extent, of the sympathetic nervous system, due to neuronal destruction associated with inflammation and the immune process caused directly or indirectly by *T. cruzi* [3, 9]. Moreover, antibodies act as neurotransmitter receptor agonists, desensitizing them and leading to neurotransmitter action blocking. Fibrosis appears slowly and gradually [17, 18].

20.4 Clinical Manifestations

The disease has two clinical presentations, an acute, usually asymptomatic one, and the other chronic, in which symptoms in the digestive or cardiac systems predominate. However, symptoms such as fever, generalized adenopathy, edema,

hepatosplenomegaly, myocarditis, and meningoencephalitis may occur in the moderate or severe forms of the disease [1, 3, 19]. The incubation period varies from 1 to 2 weeks, but in patients who acquire the disease through transplanted organs or transfused blood from infected donors, this period is longer, approximately 4 months [1, 3]. The acute form is usually mild, being fatal in less than 5% of cases [3, 4]. A small number of patients may have cardiac muscle involvement, with the development of severe myocarditis and central nervous system invasion associated with meningoencephalitis. The acute picture tends to resolve spontaneously over a period of 4–6 weeks, when the indeterminate phase of the disease starts. This phase is usually asymptomatic, showing low parasitemia associated with the production of antibodies against *T. cruzi* antigens, but many people eventually show signs of cardiac or gastrointestinal involvement before symptom onset [1, 2].

In the chronic phase of the disease, the indeterminate, cardiac, or gastrointestinal forms may occur. It usually shows a decrease in parasitemia, which occurs around 8–12 weeks after infection, if no antiparasitic therapy is initiated. Approximately 10–30% of infected individuals develop the chronic form of the disease, commonly characterized by heart disease (responsible for death due to arrhythmias or heart failure). Many patients also develop megaesophagus, megacolon, or both, characterized by dysphagia, regurgitation/reflux, and constipation [1–3]. Some patients remain in the indeterminate phase of the disease for the rest of their lives.

20.5 Diagnosis

Parasitological examinations are not routinely employed in the chronic phase of the disease due to the low parasitemia. However, serological tests that detect antibodies against *T. cruzi* can be used. The diagnosis of infection is confirmed by at least two serological tests with different techniques, and the ones most frequently used are the enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IIF), and indirect hemagglutination (IHA). The sensitivity and specificity of the first two is greater than 99.5% and between 97% and 98%, respectively. IHA tests have a sensitivity of 97–98% and specificity of 99% [1, 3].

Chronic Chagasic cardiopathy often presents with electrocardiographic alterations, the most common being complete right bundle-branch block associated with left anterior hemiblock [8, 20, 21]. Atrioventricular block (AVB), sinus node dysfunction, and non-sustained and sustained ventricular tachycardia can also be found. At more advanced stages, marked cardiomegaly with enlarged right cavities, associated with mild or absent pulmonary congestion can be seen on chest X-rays. The echocardiography allows the assessment of left and right ventricular contractile performance, presence of intracavitary aneurysms and thrombi and the presence of diastolic dysfunction [8, 20].

20.6 Kidney Involvement

20.6.1 Acute Phase

T. cruzi is characterized by the capacity to parasitize a wide variety of host cells, including kidney cells [9]. Kidney involvement is an uncommon manifestation of Chagas disease, with few studies on the subject being found in the literature [22–25]. There is evidence of kidney functional and structural alterations following *T. cruzi* infection, whether associated with decreased kidney blood flow or damage to proximal tubule cells, in addition to significant kidney inflammatory interstitial infiltrate [20, 24]. Increased kidney size is observed as being associated with a high production of proinflammatory cytokines and nitric oxide (NO). Moreover, kidney function loss may occur, especially when there is infection with high parasitic loads [22].

Acute kidney injury occurs around the sixth day of acute infection and is related to cardiovascular dysfunction, due to transient decrease in kidney blood flow, which has been demonstrated by studies showing the same injury in experimental models of ischemic and reperfusion injuries [9, 24]. The injury is unrelated to the presence or multiplication of the parasite, of which traces have been found only after 15 days of disease. Acute kidney injury is a complication described in acute Chagas disease, being an important marker of worse prognosis [9, 20].

The occurrence of glomerulonephritis in the chronic phase of the disease has been reported in *T. cruzi* infections, as well as in infections by other trypanosome species, such as the African trypanosome [23, 26–28]. The subspecies *T. brucei*, although it does not infect humans, causes disease with glomerular involvement in many mammals. Therefore, this trypanosomide is used in several experimental models to study the mechanisms involved in trypanosomiasis-induced glomerulonephritis [26, 27].

The pathophysiology of kidney impairment in Chagas disease seems to include autoimmune phenomena. The detection of a rheumatoid factor and antinuclear anti- bodies (ANA) in experimental studies with *T. cruzi*-infected rats shows that glomerular deposits in Chagas disease are not only immune complexes containing parasite antigens but also of autoantibodies. These autoantibodies manifest through polyclonal B cell activation [18].

Significant loss of kidney function was not observed in experimental studies with *T. cruzi*-

infected rats [23]. The histopathological analysis showed slight proximal tubular damage and glomerular atrophy, associated with mild inflammatory infiltrate [24]. Intracytoplasmic amastigote forms have been identified in kidney tissue of transplanted patients [29]. *T. cruzi* antigens have also been identified in the kidney graft glomerulus and interstitium in a patient with the acute form of Chagas disease [30]. Disease reactivation is important after solid-organ transplants in patients from endemic areas [7].

20.6.2 Chronic Phase

In the chronic phase of the disease, the parasitemia declines, affecting target organs such as the heart, kidneys, esophagus, and intestines, probably due to immunity disorders. However, Oliveira et al. [24] demonstrated the presence of severe kidney injury characterized by early glomerular deposition of IgM with intense inflammatory kidney response promoting the formation of immune complexes, resulting in glomerulopathy with altered kidney function.

The mechanism of immune complex deposition against *T. cruzi* antigens present in the glomerulus is not completely known [23] but seems to be mediated by immune complexes containing antigens of the parasite and rheumatoid factor (RF), demonstrated by IgM, C3, and *T. cruzi* antigen deposits in the mesangium at the immunofluorescence and characterized by electrodense deposits in the mesangial and paramesangial areas [23]. Kidney infarction has also been described in the chronic form of Chagas disease, being more common when associated with heart failure [31]. In the chronic phase of Chagas disease, there is a decrease in parasitemia, in contrast to the involvement of organs such as the heart, esophagus, intestine, and kidneys [1, 9]. Among the possible hypotheses are the ones that suggest that molecular mimicry leads to autoimmunity disorders and, finally, to the pathology in the chronic phase of the disease [18]. Several *T. cruzi* antigens, such as B13, cruzipain, and Cha, cross-react with host antigens at the B or T lymphocyte level. When mice are immunized with these antigens and/or by passive transfer of autoreactive T lymphocytes, clinical disorders similar to those found in patients with Chagas disease are found in these animals [23, 24].

Glomerular lesions in the chronic phase of Chagas disease are associated with deposits of IgM, IgG, and C3 in the mesangium, resulting in proliferation that can be visualized through immunofluorescence [24, 25]. *T. cruzi* antigens and the rheumatoid factor are found at both serum and glomerulus levels, forming complexes with IgG and C3. Although the disease progression and serum levels of parasite antigens decrease, kidney levels remain stable together with an increase in rheumatoid factor levels found in the glomeruli, thus stimulating mesangial proliferation [24]. This increase in mesangial cells is mediated by a secondary immune complex deposition [24]. Thus, the most common trypanosome-associated lesions are the mesangial proliferative glomerulonephritis and membranoproliferative glomerulonephritis [23, 24]. Electron microscopy can disclose electrodense deposits [23, 24]. Kidney infarction has also been described in the chronic form of Chagas disease [31]. In a necropsy review of 78 patients with the chronic form of Chagas disease, 24.4% developed kidney infarction, which was more frequent among those with heart failure, 52.6% [31].

The pathophysiology of kidney involvement in Chagas disease is shown in Fig. 20.1.

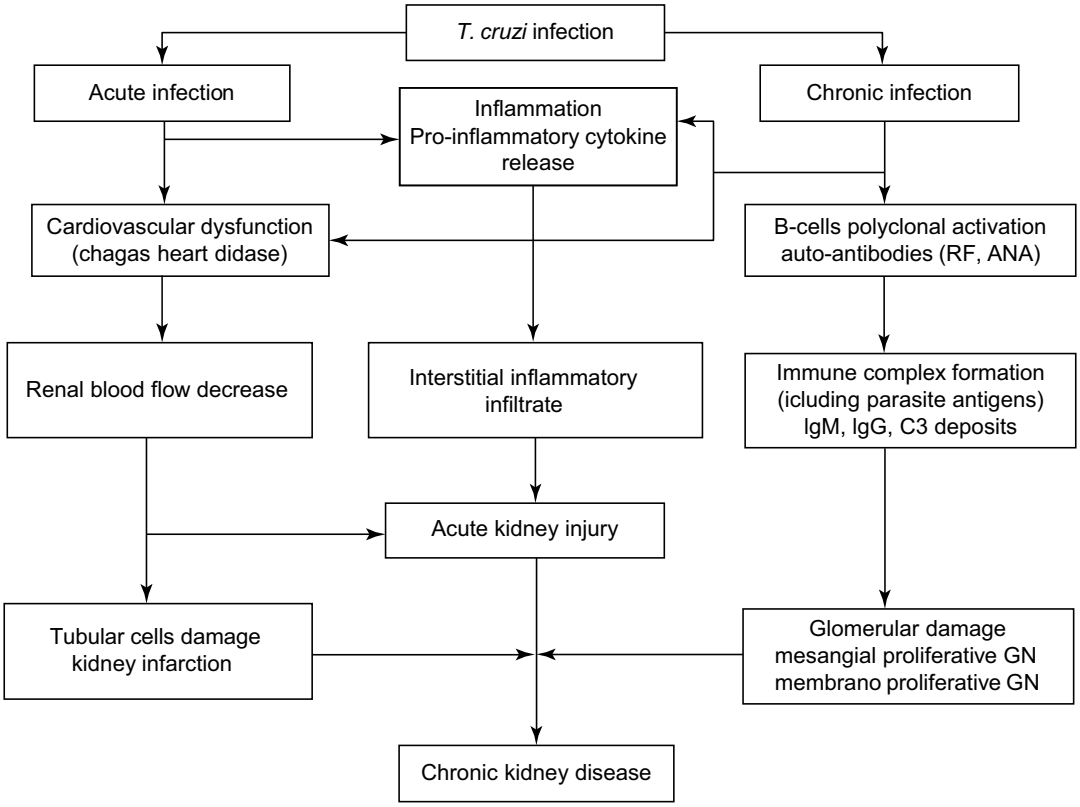


Fig. 20.1 Pathophysiology of kidney involvement in Chagas disease. *RF* rheumatoid factor, *ANF* antinuclear factor, *GN* glomerulonephritis. (Adapted from Silva Junior et al. [9], with permission. © 2017 Sociedad Latinoamericana de Nefrología e Hipertensión)

20.7 Treatment

The treatment of Chagas disease includes supportive treatment, such as withdrawal from professional, school, or sports activities, at medical discretion, free diet, and avoiding alcoholic beverages. The specific treatment is carried out with benznidazole, which is the drug of choice. Nifurtimox can be used as an alternative, in cases of intolerance to benznidazole [13].

In the acute phase, the treatment should be carried out in all cases and as soon as possible after diagnostic confirmation. The specific treatment is effective in most acute cases (the cure is achieved in more than 60% of cases). The specific treatment aims at curing the infection, preventing organ damage or its evolution, and decreasing the possibility of *T. cruzi* transmission [13, 32]. Benznidazole is sold as 100-mg tablets and 2 or 3 daily doses should be taken for 60 days [13, 32].

Recommended doses:

Benznidazole

- Adults: 5 mg/kg/day orally, divided into 2–3 daily doses for 60 days. The maximum recommended dose is 300 mg/day.
- Children: 5–10 mg/kg/day and infants 10 mg/kg/day.
- Note: 100 mg tablets and 12.5 mg/tablet are available from the public health network.

Nifurtimox

- Adults: 8–10 mg/kg/day orally, divided into 3 daily doses for 60 days.
- Children: 15 mg/kg/day orally, divided into 3 daily doses for 60 days.
- Note: 120-mg tablets (adults) and 30-mg tablets (children).

In patients with the indeterminate form of the disease or already established Chagasic cardiopathy, the indication of specific treatment is controversial. There is experimental evidence suggesting the attenuation of cardiopathy progression [33, 34].

References

1. Maguire JH. Trypanosoma. In: Gorbach S, Bartlett J, Blacklow N, editors. Infectious diseases. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 2004. p. 2327–34.
2. Teixeira ARL, Nascimento R, Sturm NR. Evolution and pathology in Chagas disease—a review. Mem Inst Oswaldo Cruz. 2006;101(5):463–91.
3. Pérez-Molina JA, Molina I. Chagas disease. Lancet. 2018;391:82–94.
4. Beltrão HB, Cerroni MP, Freitas DR, et al. Investigation of two outbreaks of suspected oral transmission of acute Chagas disease in the Amazon region, Para State, Brazil, in 2007. Trop Dr. 2009;39(4):231–2.
5. Riarte A, Luna C, Sabatiello R, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989–1996. Clin Infect Dis. 1999;29:561–7.
6. Bem C, Martin DL, Gilman RH. Acute and congenital Chagas disease. Adv Parasitol. 2011;75:19–47.
7. Centers for Disease Control and Prevention (CDC). Chagas disease after organ transplantation—United States, 2001. MMWR Morb Mortal Wkly Rep. 2002;51:210–2.
8. Kun H, Moore A, Mascola L, et al. Transmission of *Trypanosoma cruzi* by heart transplantation. Clin Infect Dis. 2009;48:1534–40.
9. Silva Junior GB, Antunes VVH, Motta M, Barros EJG, Daher EF. Chagas disease-associated kidney injury—a review. Nefrol Latinoam. 2017;14(1):22–6.
10. Kirchhoff LV. American trypanosomiasis (Chagas' disease)—a tropical disease now in the United States. N Engl J Med. 1993;329:639–44.
11. Dias JCP. Globalization, inequity and Chagas disease. Cad Saúde Pública (Rio de Janeiro). 2007;23:S13–22.
12. Vinhaes MC, Dias JCD. Doença de Chagas no Brasil. Cad Saúde Pública (Rio de Janeiro). 2000;16(Supp. 2):7–12.
13. Cardoso AVN, Lescano SAZ, Amato Neto V, Gakiya E, Santos SIV. Survival of Trypanosoma Cruzi in sugar cane used to prepare juice. Rev Inst Med Trop Sao Paulo. 2006;48(5):287–9.
14. Bastos CJC, Aras R, Mota G, Reis F, Dias JP, Jesus RS, Freire MS, Araújo EG, Prazeres J, Grassi MF. Clinical outcomes of thirteen patients with acute Chagas disease acquired through oral transmission from two urban outbreaks in northeastern Brazil. PLoS Negl Trop Dis. 2010;4(6):e711.
15. Dias JCP, Ramos Junior AN, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, et al. II Consenso Brasileiro em Doença de Chagas, 2015. Epidemiol Serv Saúde. 2016;25(n. spe):7–86.
16. Andrade ZA. Patologia da Doença de Chagas (Portuguese). In: Brener Z, Andrade ZA, Barral-Netto M, editors. *Trypanosoma cruzi* e Doença de Chagas. 2nd ed. Rio de Janeiro: Guanabara Koogan; 2000. p. 201–30.
17. Tarleton RL. Chagas disease: a role for autoimmunity? Trends Parasitol. 2003;19(10):447–51.
18. Hyland KV, Engman DM. Further thoughts on where we stand on the autoimmunity hypothesis of Chagas disease. Trends Parasitol. 2006;22(3):101–2.
19. Coura JR. Chagas disease: what is known and what is needed—a background article. Mem Inst Oswaldo Cruz (Rio de Janeiro). 2007;102:113–22.
20. Cumbinho LC, Pizzini CC, Oliveira FS, Batista W, Oliveira GM. Cardiorenal interaction during the acute phase of experimental *Trypanosoma cruzi* infection: the influence of aldosterone and the AT1 receptor on mortality. J Exp Integr Med. 2012;2(3):199–206.
21. Pinto AY, Valente SA, Valente VC. Emerging acute Chagas disease in Amazonian Brazil: case reports with serious cardiac involvement. Braz J Infect Dis. 2004;8:454–60.
22. Lemos JRD, Rodrigues WF, Miguel CB, Parreira RC, Miguel RB, Rogerio AP, et al. Influence of parasite load on renal function in mice acutely infected with *Trypanosoma cruzi*. PLoS One. 2013;8(8):e71772.
23. Costa RS, Monteiro RC, Lehuen A, Joskowicz M, Noël LH, Droz D. Immune complex- mediated glomerulopathy in experimental Chagas' disease. Clin Immunol Immunopathol. 1991;58:102–14.
24. Oliveira GM, da Silva TM, Batista WS, Franco M, Schor N. Acute *Trypanosoma cruzi* experimental infection induced renal ischemic/reperfusion lesion in mice. Parasitol Res. 2009;106:111–20.
25. Oliveira GM, Masuda MO, Rocha NN, Schor N, Hooper CS, Araújo-Jorge TC, Henriques-Pons A. Absence of Fas-L aggravates renal injury in acute *Trypanosoma cruzi* infection. Mem Inst Oswaldo Cruz. 2009;104:1063–71.
26. Bruijn JA, Oemar BS, Ehrich JH, Oemar BS, Ehrich JM. Anti-basement membrane glomerulopathy in experimental trypanosomiasis. J Immunol. 1987;139:2482–8.

27. van Velthuysen MLF, Bruijn JA, van Leer EHG, Fleuren GJ. Pathogenesis of trypanosomiasis-induced glomerulonephritis in mice. Nephrol Dial Transplant. 1992;7:507–15.
28. Rickman WJ, Cox HW. Association of autoantibodies with anemia, splenomegaly, and glomerulonephritis in experimental African trypanosomiasis. J Parasitol. 1979;65:65–73.
29. Arias LF, Duque E, Ocampo C, et al. Detection of amastigotes of *Trypanosoma cruzi* in a kidney graft with acute dysfunction. Transplant Proc. 2006;38:885–7.
30. Silva AE, Silva AC, Faleiros AC, et al. Acute Chagas' disease in postrenal transplant and treatment with benznidazole. Ann Diagn Pathol. 2010;14:199–203.
31. Mohallem SV, Ramos SG, dos Reis MA, Seabra DD, Teixeira VP. Prevalence of renal infarcts in autopsies of chronic Chagas disease patients. Rev Soc Bras Med Trop. 1996;29:571–4.
32. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Coordenação-Geral de Desenvolvimento da Epidemiologia em Serviços. Guia de Vigilância em Saúde. 1st ed. Brasília: Ministério da Saúde; 2017.
33. Coura JR, Borges-Pereira J. Chronic phase of Chagas disease: why should it be treated? A comprehensive review. Mem Inst Oswaldo Cruz. 2011;106(6):641–5.
34. Viotti R, Alarcón de Noya B, Araujo-Jorge T, et al. Towards a paradigm shift in treatment of chronic Chagas disease. Antimicrob Agents Chemother. 2014;58(2):635–9.

21 Kidney Disease Associated with *Schistosomiasis Mansoni*

Daniella Bezerra Duarte,
Elizabeth De Francesco Daher,
Maria Eliete Pinheiro,
and Michelle Jacintha Cavalcante Oliveira

21.1 Introduction

Schistosomiasis is a chronic parasitic disease caused by trematodes of the genus Schistosoma, of which five species parasitize humans: *S. mansoni*, *S. japonicum*, *S. haematobium*, *S. intercalatum,* and *S. mekongi*. The disease is endemic in tropical regions, where there are currently millions of people living in areas at risk of transmission. In Brazil, only S. mansoni is found in 19 states, with the highest endemicity observed in the northeastern states [1, 2].

Kidney disease related to schistosomiasis is not often described in the literature, and most studies show an association between the disease and glomerular alterations, especially in those patients with a more severe clinical presentation. However, other forms of kidney involvement and new biomarkers of kidney damage have been described in recent years. In this chapter, we will review the general aspects of the disease and describe the characteristics of renal involvement in schistosomiasis mansoni.

21.2 Epidemiology

Schistosomiasis is a tropical disease currently present in around 70 countries, mainly in Africa, the Eastern Mediterranean, and South America. A total of 200 million people are estimated to be infected, 85% of whom live in sub-Saharan Africa, approximately 120 million develop symptoms, 20 million have severe disease, and 100,000 die each year [3, 4]. It was brought over by African slaves and spread to South and Central America and the Caribbean region. It was first detected by the doctor Augusto Pirajá da Silva in the state of Bahia. It is classified by the WHO as one of the neglected tropical diseases [5] and continues to be one of the most important parasitic diseases in the tropics and subtropics, constituting an important public health problem [6, 7].

Schistosoma species vary according to geographical area. *S. mansoni* occurs in South America, the Caribbean islands, and, together

D. B. Duarte
School of Medicine, Universidade Federal de Alagoas, Maceió, Alagoas, Brazil

School of Medicine, Centro Universitário de Maceió, Maceió, Alagoas, Brazil

School of Medicine, Centro Universitário CESMAC, Maceió, Alagoas, Brazil

E. De Francesco Daher
Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

M. E. Pinheiro (✉) · M. J. C. Oliveira
School of Medicine, Universidade Federal de Alagoas, Maceió, Alagoas, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_21

with S. haematobium, in Africa and the Middle East. *S. haematobium* is also observed in parts of West and Central Africa. *S. japonicum* and *S. mekongi* occur in several Southeast Asian countries, and *S. japonicum* is also found in China and the Philippines. Transmission is focal in endemic countries and more intense in poor rural areas with inadequate sanitation and no water supply [4].

In the Americas, schistosomiasis is most prevalent in the Caribbean region, Venezuela, and Brazil, where the disease is endemic [4]. Despite efforts to control it, Brazil is the South American country with the highest number of registered cases, with an estimated 4.6% of the population affected, or approximately eight million people [8–10]. It has been described in almost the entire national territory, but with a higher prevalence in the northeastern states. Its occurrence is directly related to the presence of the transmitting snail. It is estimated that there are 25 million people in the country at risk of contracting the disease [11]. Minas Gerais was the state in Brazil with the highest number of confirmed cases of the disease in 2022, accounting for 53.6% of all cases in the country that year. In 2022, 2736 cases were recorded throughout Brazil, 1815 in the Southeast and 789 in the Northeast, according to data from DATASUS [12]. Studies have shown a reduction in the prevalence of schistosomiasis in Brazil over seven decades, which can be explained by a combination of community, demographic, socioeconomic, and environmental factors [13].

The disease is associated with high morbidity and mortality, with chronic complications usually seen in people with a high parasite load, which generally occurs in those living in endemic areas and subjected to repeated exposure [14]. Figure 21.1 shows the distribution of schistosomiasis in Brazil according to the percentage of positivity in coproscopic surveys in 2012 [15].

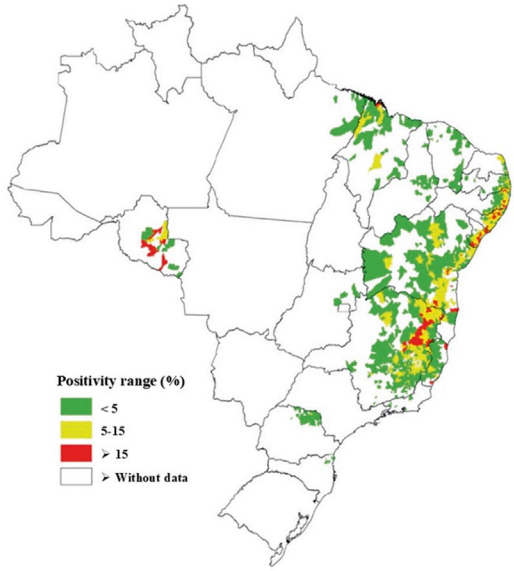


Fig. 21.1 Distribution of schistosomiasis in Brazil according to the percentage of positivity in coproscopic surveys [15]. (Source: Schistosomiasis Surveillance and Control Program Information System—SISPCE/SVS/MS)

21.3 Evolutionary Cycle

The evolutionary cycle of *S. mansoni* is complex and requires an intermediate and a definitive host. Man is the definitive host of *S. mansoni*. The intermediate host is the snail, an aquatic mollusk of the Planorbidae family, included in the *Biomphalaria* genus, whose natural habitat is freshwater streams with little or no current, small lakes, marshes, irrigation ditches, vegetable gardens, and others [8].

Once disposed of in water, *S. mansoni* eggs hatch, releasing the miracidium, which penetrates the intermediate host, the snail. The miracidium reproduces asexually until it turns into a cercarial larva (the infective form). The cercariae leave the snail and penetrate the intact skin of humans, transforming into schistosomes, which migrate to the lungs and liver. After around six weeks, they

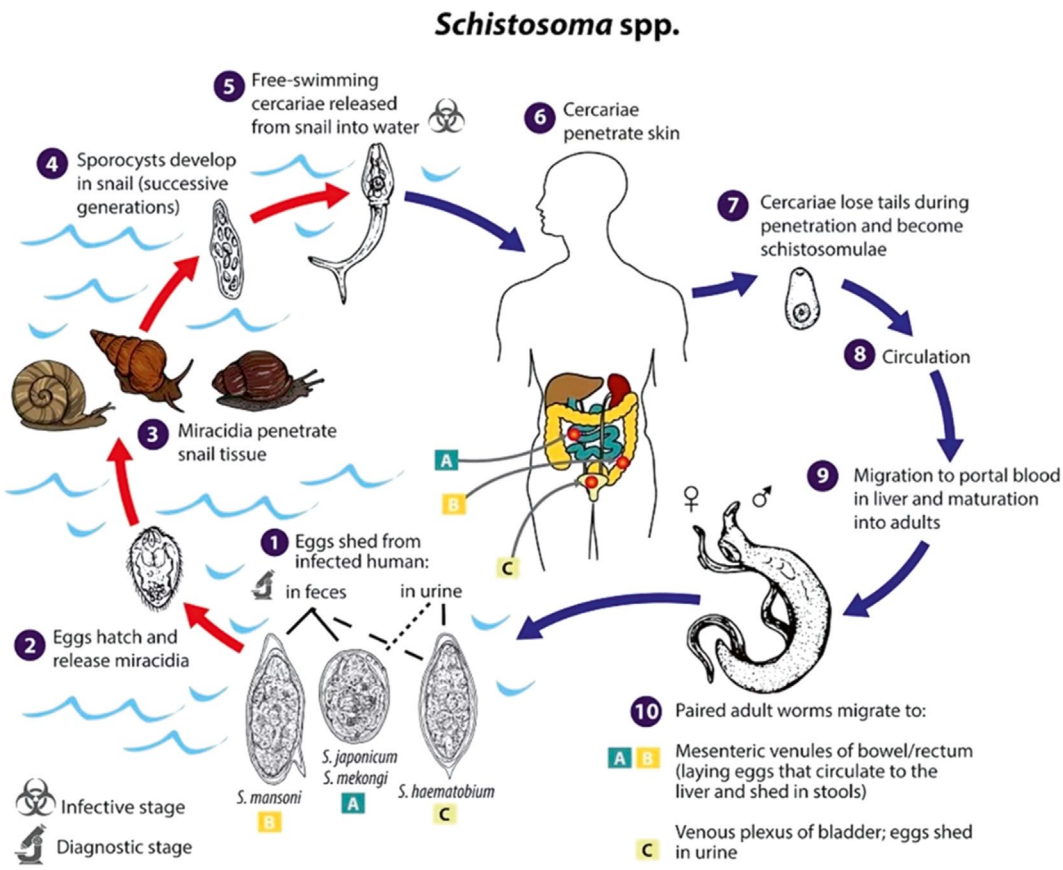


Fig. 21.2 Evolutionary cycle of *Schistosoma mansoni*. (Source: Centers for Disease Control and Prevention: https://www.cdc.gov/dpdx/schistosomiasis/index.html)

evolve into the adult form and migrate to the portal system [16].

After 1–3 months, the female worm begins to produce eggs, which can travel hematogenously to other sites or cross the intestinal wall, reaching the intestinal lumen and then being excreted in the feces [1, 17]. Eggs released into the bloodstream by adult worms can invade local tissues, where they release toxins and enzymes and provoke a TH-2-immune-mediated response [18]. Inflammation and granuloma formation occur around the deposited eggs, which can lead to fibrosis of the affected tissues [19]. Figure 21.2 summarizes the evolutionary cycle of S. mansoni.

21.4 Clinical Manifestations

The clinical presentation of schistosomiasis results from the host's immune response to Schistosoma eggs and the granulomatous reaction evoked by the antigens they secrete. Depending on the parasite load of each individual and their immune response, a wide range of clinical forms can be expressed, from asymptomatic forms to acute manifestations and chronic forms. The evolution depends on the immune response, the development of the worm, and its oviposition [2]. The immune response of individuals with schistosomiasis includes humoral as well as cellular components. The degree and extent of this

response provide the balance between asymptomatic infestation and the manifestations of the disease [1].

Most individuals exhibit the mild forms of the disease (asymptomatic, intestinal, and hepatointestinal). The hepatosplenic form, on the other hand, is found in between 4% and 7% of those infected and is associated with heavy parasite infestation [2, 17]. Acute symptoms are more common in nonimmune people, such as travelers, due to a more intense immune response to exposure. On the other hand, chronic complications require a greater burden of infection and are therefore seen mainly in individuals from endemic areas [20].

The acute phase occurs several weeks after the penetration of the cercariae and is considered a toxemic allergic reaction to the migration and maturation of the *S. mansoni* larvae. In general, the symptoms are fever, dry cough, weakness, headache, abdominal symptoms, urticaria, and/or angioedema. The severity of the clinical picture varies according to the parasite load and the immune response to parasite antigens, and circulating immune complexes are found in 55–93% of patients with acute schistosomiasis [21].

The chronic phase can be divided into three clinical forms: intestinal, hepatointestinal and hepatosplenic [22]. In the intestinal form, the most common symptoms include chronic or intermittent abdominal pain, loss of appetite, and diarrhea [23]. Intestinal polyps can appear around the granulomatous inflammation surrounding the eggs deposited in the intestinal wall. Intestinal ulcers can also develop. Rarely, an inflammatory mass can lead to obstruction [24]. In the majority of cases, symptoms remain mild as long as the parasite load is low and the accumulation of eggs in the tissues is small. In this form, liver damage is moderate and the symptoms—such as loss of appetite, abdominal discomfort, asthenia, intestinal cramps, diarrhea, and dysentery—are generally mild and quite variable and can persist for years due to the difficulty of diagnosis, as well as symptoms similar to other types of disease [25, 26].

As the eggs are carried through the circulation and lodge in the liver, the parasitosis worsens, leading the patient to develop the hepatointestinal form. Although the symptoms of both forms are similar, the liver lesions in the hepatointestinal form are more intense than in the intestinal form, with a slightly palpable spleen and liver. The clinical picture can evolve, and the patient develops the hepatosplenic form, which is characterized by involvement and considerable enlargement of the liver and spleen [25].

In the hepatosplenic form, patients can be asymptomatic and are recognized on clinical examination by the presence of left hepatomegaly and splenomegaly. They often have gastrointestinal complaints, such as dyspepsia, flatulence, or diarrhea. Portal hypertension, caused by Symmers' liver fibrosis, a typical finding of the hepatosplenic form, is the basis of the pathogenesis, leading to clinical consequences such as the appearance of varicose veins of the submucosal plexus of the esophagus and stomach, and splenomegaly, with hypersplenism, leading to hematological alterations such as thrombocytopenia and leukopenia [17]. Many patients remain in their stationary or compensated clinical form, maintaining a good general condition, with minor symptoms, but they can evolve into the decompensated hepatosplenic form [27]. Generally, this decompensation occurs after an episode of digestive bleeding, which can lead to transient liver failure, characterized by ascites, peripheral edema, mild jaundice, and encephalopathy [17]. Mortality from schistosomiasis occurs mainly in this form. The rupture of esophageal varices leads to severe digestive bleeding, which is often fatal [28, 29].

There are still other chronic forms of schistosomiasis, such as the vasculopulmonary form, characterized by pulmonary hypertension and presenting as cor pulmonale; glomerulopathy, which will be discussed in depth later in this chapter; and the neurological form, caused by the presence of eggs and schistosomal granulomas in the central nervous system, with transverse myelitis being the most frequent lesion in these cases. In addition, other less common locations can also be affected by schistosomiasis, such as the female genital organs, testicles, skin, retina, thyroid, and heart, and it can appear in any organ

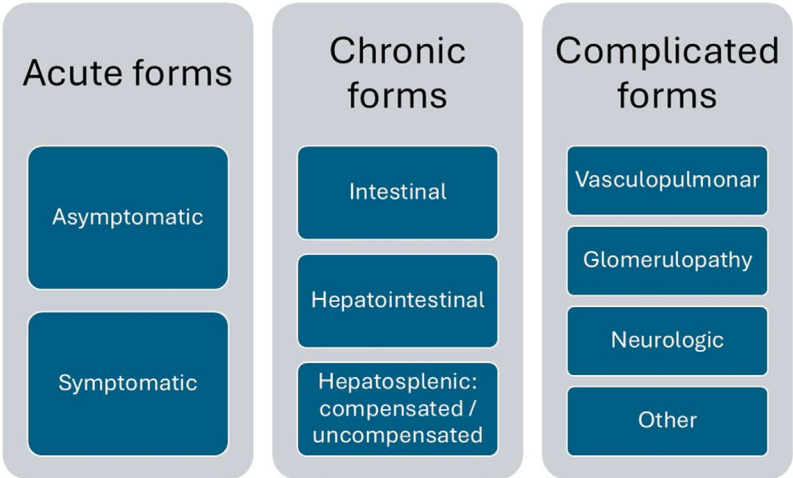


Fig. 21.3 Clinical forms of *Schistosomiasis mansoni*

Table 21.1 Diagnostic methods for Schistosomiasis mansoni

Direct methods	Indirect methods	Imaging diagnosis
Fecal egg search	Serologies	Abdominal ultrasound
Kato-Katz	ELISA	Upper gastrointestinal endoscopy
HPJ	Immunofluorescence	Medullary magnetic ressonance
Miracidia hatching	Periovular reaction	Doppler ecocardiogram
Circulating parasite antigen search	Intradermoreaction	
Capture ELISA		
Retal, hepatic and Other places' biopsy		

or tissue of the human body [30]. Figure 21.3 summarizes the main clinical forms of schistosomiasis.

21.4.1 Diagnosis

The diagnosis of *Schistosomiasis mansoni* is based on the patient's history, combined with the fact that he or she is from or has lived in a region recognized as endemic, associated with laboratory and imaging tests.

Laboratory tests can show the presence of *S. mansoni* eggs in feces or tissues or circulating antigens of the parasite (direct methods) [30, 31]. Indirect methods, on the other hand, are based on immunological mechanisms, detect antibodies, and, when positive, do not necessarily indicate active infection, since positivity, due to the presence of antibodies, can remain for many years, even after the infection has been cured [30].

Although imaging tests do not identify the parasite, they are extremely important for identifying the damage caused by *S. mansoni* and for differential diagnosis. Abdominal ultrasound, for example, has proven its value in diagnosing the hepatosplenic form of schistosomiasis mansoni, showing characteristic signs of Symmers fibrosis, as well as providing information on the size of the liver and spleen and the caliber of the portal vessels [30]. Table 21.1 summarizes the main methods for diagnosing *Schistosomiasis mansoni*.

21.5 Kidney Involvement in *Schistosomiasis mansoni*

21.5.1 Schistosomal Glomerulopathy

There is no consensus on the prevalence of kidney involvement in schistosomiasis, which varies according to the series evaluated and the geo-

graphical factors that seem to influence the different patterns of glomerular injury [32]. In Brazil, the incidence of glomerular disease in schistosomiasis has been described as varying between 5 and 6%, a percentage that rises to 15% when only patients with the hepatosplenic form of the disease are considered [33].

Some authors suggest that kidney disease associated with schistosomiasis is decreasing in Brazil, as a result of therapeutic interventions in endemic areas that began in the late 1970s. However, a cross-sectional study designed to update the prevalence of kidney disease in patients with hepatosplenic schistosomiasis in a reference center in Minas Gerais from 2007 to 2009 evaluated 63 patients with *Schistosomiasis mansoni* and found evidence of kidney involvement in 12.7% of patients, corroborating the idea that the prevalence has not decreased [34]. Subsequently, a study carried out in the city of Salvador found a reduction in the frequency of membranoproliferative glomerulonephritis (MPGN) from 20% in 1975 to 6% in 2017, suggesting that this reduction may be associated with a decrease in cases of schistosomiasis since the cases of MPGN described in that city in 1975 were almost entirely secondary to schistosomiasis [35, 36].

21.5.2 Pathophysiology

The immunological nature of glomerular lesions is well established and depends on the release of antigenic molecules produced by the parasite, triggering the formation of immune complexes that are deposited in the glomeruli [16, 37].

Among the various antigens isolated, those from the adult worm's digestive tract, of a polysaccharide nature, regurgitated by the parasite, are those implicated in the pathogenesis of glomerulopathy [38]. Two main antigens of *Schistosoma mansoni*, the circulating anodic antigen (CAA) and the circulating cathodic antigen (CCA), have been ultrastructurally localized in glomerular deposits of humans and experimental animals infected with S. Mansoni [39, 40]. CAA and CCA are bound by the glomerular basement membrane and deposited in the mesangial matrix. CAA was seen in considerably smaller quantities than CCA, this being attributed to the fact that CAA, but not CCA, is repelled by the negative charge of the glomerular basement membrane [41].

Although antigens from the adult worm are the most closely related to schistosomal glomerulopathy, soluble egg antigens also contribute to the pathogenesis of glomerulopathy, as demonstrated in experimental studies, where soluble egg antigens were ultrastructurally localized by immunomicroscopy in the glomeruli of hamsters injected with S. mansoni eggs [42].

Other important factors, in addition to the production of antigens by the adult worm, seem to contribute to the genesis of glomerular disease in schistosomiasis mansoni, such as collateral circulation of the portal system due to the degree of liver involvement, the inefficiency of the liver's macrophage system, the severity and duration of the infestation, as well as racial and genetic factors [34, 41]. Portal hypertension, with collateral circulation, facilitates the passage of schistosomal antigens, which bind to antibodies in the circulation and are subsequently deposited in the glomeruli [43].

Immunoglobulin A (IgA) has also been suggested as a mediator of glomerular lesions in more advanced stages of the disease, but the relevance of this data is still debatable. It is believed that portal hypertension and liver damage with inefficiency of the hepatic macrophage system play a fundamental role, allowing both schistosomal antigens and IgA polymers to escape hepatic clearance [41, 43].

Glomerular damage is also related to the intensity of the parasitosis and the type and duration of the process. Trials with rats infected with different amounts of cercariae showed significant proteinuria, hypoalbuminemia and hypercholesterolemia in those infected with 50 cercariae or more, but not in the controls or the group infected with 20 cercariae, and there seems to be a significant correlation between the pathological alterations and the duration and load of *S. mansoni* infection [44]. The pathophysiology of glomerular damage in schistosomiasis is illustrated in Fig. 21.4.

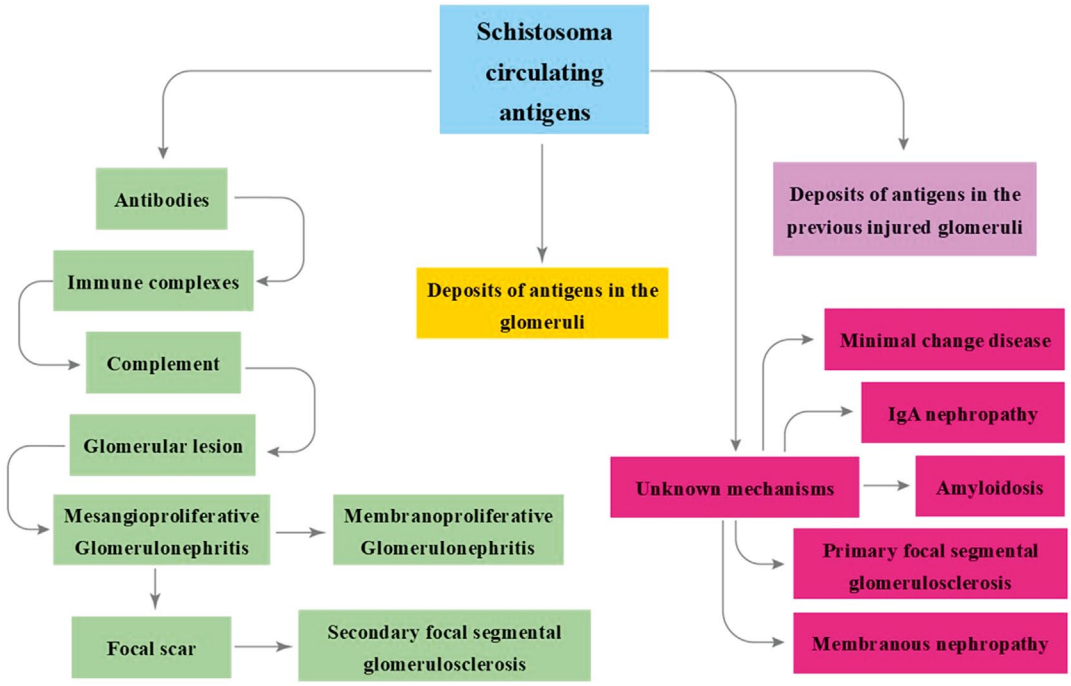


Fig. 21.4 Pathophysiology of glomerular lesions associated with schistosomiasis. (Adapted from Nussenzveig et al. [48])

21.6 Histopathological Findings

Traditionally, five classes of schistosomiasis-related glomerulopathy are recognized: Class I, mesangioproliferative glomerulonephritis, is associated with the deposition of immune complexes containing schistosomal antigens, IgM and C3. Class II, exudative glomerulonephritis, is characterized by neutrophils, monocytes, and eosinophils invading the mesangium, as well as subendothelial and mesangial deposits of C3, often associated with IgG and IgM. It occurs concomitantly with *Schistosoma* infection and *Salmonella* species. Class III is a membranoproliferative glomerulonephritis, while class IV is a segmental and focal sclerosing lesion. These two classes make up the majority of patients with progressive disease and correlate with the degree of associated schistosomal liver fibrosis. They are often associated with abnormalities in serum IgA components, as well as glomerular and peritubular IgA deposits. Class V, amyloidosis, stems from a generalized response to chronic inflammation and occurs in cases of prolonged infection [45]. Figure 21.5 illustrates membranoproliferative glomerulonephritis associated with schistosomiasis.

Membranous nephropathy (MN) is also found in patients with schistosomiasis. A study that analyzed immunopathological data from 12 patients with MN showed, unexpectedly, positivity for IgG1 in 91.7% of patients and for IgG4 and PLA2R in 83.3%, suggesting a pattern of primary glomerulopathy [46].

It is believed that the patterns of glomerular damage described in schistosomiasis reflect the influence of geographical factors and perhaps pathogenetic differences. Amyloidosis, for example, is rarely seen in Brazil as a complication of advanced schistosomal glomerulopathy, as are IgA glomerular deposits seen in African series [47, 48].

Membranoproliferative glomerulonephritis and segmental and focal glomerulosclerosis

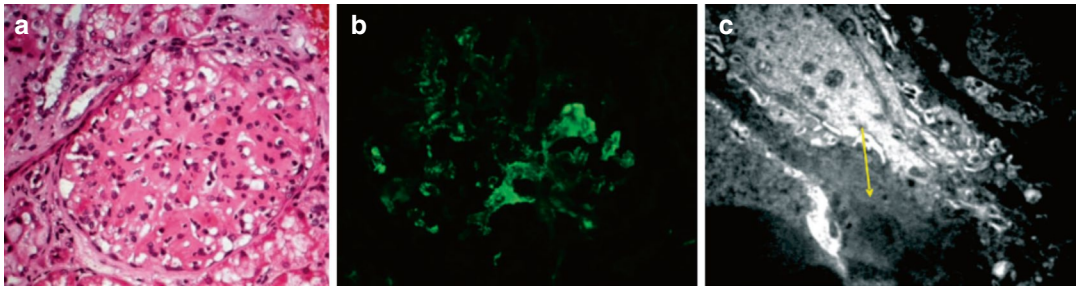


Fig. 21.5 Renal histopathological findings in schistosomiasis. (**a**) Optical microscopy of a patient with membranoproliferative glomerulonephritis type I; (**b**) Immunofluorescence showing glomerular IgG deposits; (**c**) Electron microscopy showing electron-dense deposits (arrow) in the glomerular basement membrane [33]

(FSGS) represent the glomerular lesion patterns most consistently associated with the hepatosplenic form of schistosomiasis in Brazil. Both are associated with nephrotic syndrome and progression to chronic kidney disease [34, 49–51].

21.6.1 Clinical Picture

Classically, schistosomal nephropathy is associated with the hepatosplenic form of schistosomiasis; however, it is also seen in its hepatointestinal forme. In general, patients are young adults, of both sexes, living in areas endemic for the disease [27]. They may present on physical examination with hepatomegaly with prominence of the left lobe and, in most cases, splenomegaly [52].

The clinical presentation of schistosomal nephropathy is variable, with nephrotic syndrome being the most common clinical presentation [27]. One peculiarity is that it presents with normal cholesterol levels in 33% of cases and hyperglobulinemia in 26%. Proteinuria is of low selectivity. In addition to nephrotic syndrome, other manifestations of schistosomal nephropathy include hypocomplementemia, microalbuminuria, or non-nephrotic proteinuria [53, 54].

Initially, the glomerular lesion may be asymptomatic or only manifest as hypocomplementemia. The behavior of C3 is variable, decreasing in 45–80% of cases [53, 55]. In our service, hypocomplementemia was found in 50% of hepatosplenic patients, and there was no correlation between complement levels and renal function parameters, especially proteinuria and microalbuminuria, reinforcing the idea that hypocomplementemia may be an initial manifestation of schistosomal nephropathy [56].

Non-nephrotic proteinuria can be present in up to 25% of patients with the hepatosplenic form and 5% in the hepatointestinal form 22 [57]. In our service, 24-hour proteinuria above 150 mg/day was present in 25% of hepatosplenic patients. Significant microalbuminuria (>30mg/day), which is a known early marker of glomerular damage, was found in 20% of our hepatosplenic patients [56]. Another study evaluated the presence of microalbuminuria in schistosomiasis, comparing microalbuminuria levels between treated and untreated *S. mansoni*-infected patients and a healthy control group, and found no difference between the three groups [58].

The prevalence of chronic kidney disease (CKD) in patients with schistosomiasis is unclear. A small proportion of patients may present with advanced kidney failure, and around 30–40% of patients have hypertension at the time of diagnosis of kidney disease [53]. The disease is progressive and is not influenced by therapy with antiparasitic drugs or immunosuppressants [59].

21.7 Other Forms of Renal Involvement in Schistosomiasis

21.7.1 A Tubular Changes

Unlike what occurs with schistosomal glomerulopathy, tubular involvement in schistosomiasis has not been described in the literature. In our facility, studying patients with compensated hepatosplenic schistosomiasis (HSS) with preserved glomerular filtration, and similar to what happens in other infectious diseases such as American cutaneous leishmaniasis, kala-azar, and leprosy [60–62], we found a high incidence of tubular alterations, with urinary concentration impairment present in 85% of cases and urinary acidification deficit in 45%. Urine osmolality and the urinary-to-plasma osmolality ratio also appear to be lower in patients with HSS. Urine pH, in turn, was significantly higher in patients with HSS compared to controls, suggesting that these patients may present with distal renal tubular acidosis. A subsequent study that evaluated the expression of tubular transporters through the analysis of urinary exosomes from these patients showed a decrease in aquaporin-2 expression and an increase in NKCC2 expression, which could explain the urinary concentration impairment [63].

The mechanism by which patients with HSS exhibit urinary concentration and acidification deficits is not clear, but it may also be related to immunological components activated by the parasitic infection.

21.8 Acute Kidney Injury

There are no reports describing acute kidney injury (AKI) in patients with schistosomiasis, and therefore, its pathophysiology is not fully understood. We conducted a retrospective study in our facility with 60 patients with hepatosplenic schistosomiasis who were hospitalized after a clinical decompensation of the disease. AKI was defined according to the RIFLE criteria and was present in 43.3% of patients during hospitalization. Older age, longer hospitalization, presence of ascites, and use of diuretics were conditions associated with AKI. Death occurred in 5 cases, 4 of which were in the AKI group. The Child-Pugh and MELD [64, 65] scores, used to assess the severity and prognosis of chronic liver disease, were higher among patients with AKI [66].

Acute kidney injury appears to be an important feature of decompensated schistosomiasis and is associated with significant morbidity and mortality [66]. However, the mechanisms through which schistosomiasis may lead to acute kidney dysfunction are unclear, whether due to mechanisms related to the transient liver failure observed in these patients or due to some additional mechanism related to chronic infection.

21.8.1 New Biomarkers of Kidney Injury

The search for new renal biomarkers is extremely important, as it can provide early diagnosis of kidney alterations, allowing for the adoption of measures that may prevent progression to end-stage chronic kidney disease. Monocyte chemoattractant protein-1 (MCP-1), a chemokine that acts as a potent activator of monocytes/macrophages [67], is suggested as one of these new biomarkers and appears to play an important role in the pathogenesis of progressive renal insufficiency and various types of kidney diseases, based on observations from several animal and human models [68].

An observational study evaluated, for the first time, urinary MCP-1 levels in schistosomiasis, finding a significant increase in this biomarker in the urine of patients with active and treated *Schistosomiasis mansoni* compared to the control group, as well as a correlation between urinary MCP-1 levels and microalbuminuria. Even though no difference was observed between the groups regarding urinary albumin excretion rate, an increase in urinary MCP-1 was noted in patients with active or treated *S. mansoni* infection, suggesting that the infection may induce a state of chronic kidney inflammation that is not interrupted by specific

treatment of the causative agent [58]. In our facility, we compared urinary MCP-1 levels of patients with compensated hepatosplenic schistosomiasis and a control group of healthy individuals, finding higher urinary MCP-1 levels in patients with schistosomiasis. Additionally, there was a positive correlation between MCP-1 levels and microalbuminuria and 24-hour proteinuria in patients with schistosomiasis. The finding of a difference in MCP-1 levels, but not in microalbuminuria and proteinuria levels when comparing the schistosomiasis group with the control group, may suggest a role for MCP-1 in the earlier detection of renal damage associated with schistosomiasis [56].

21.9 Evolution and Treatment

Treatment with antiparasitic drugs, such as oxamniquine or praziquantel, is indicated in all cases where there is evidence of active disease, unless contraindicated. It offers benefits such as symptom improvement, a sense of well-being, reduction in liver and spleen size, and decrease in hepatic fibrosis [4, 54, 69]. Praziquantel is available in 600 mg tablets and is administered orally in a single dose of 50 mg/kg of body weight for adults and 60 mg/kg for children. For oxamniquine, the recommended doses are 20 mg/kg for children and 15 mg/kg for adults. Both medications should be taken at once, about 1 hour after a meal [30].

The treatment of severe acute schistosomiasis should begin with prednisone (1 mg/kg of body weight/day), followed by antiparasitic treatment (oxamniquine or praziquantel) 24–48 h later [30]. Regarding portal hypertension, surgical treatment is employed in hepatosplenic schistosomotic patients who present with upper gastrointestinal hemorrhage, with splenectomy associated with left gastric vein ligation or azygoportal disconnection with splenectomy being the most commonly used techniques [17, 30].

Concerning renal involvement, some studies suggest that kidney lesions are irreversible, as many cases are diagnosed late. However, specific antiparasitic treatment may alter the development of kidney disease or its progression when initiated in the early stages. Patients with proliferative forms do not respond to antiparasitic treatment or immunosuppression, suggesting that this type of glomerular involvement follows a progressive pattern [53].

Once the clinical picture has developed, glomerulopathy is already advanced and irreversible, at a stage where non-immunological mechanisms of renal disease progression are activated and no longer depend on the presence or absence of the parasite. It is possible that antiparasitic treatment in the early stages of the disease, in patients without clinical manifestations of renal disease, may alter the development or progression of nephropathy [53, 54].

The progression of patients with focal segmental glomerulosclerosis secondary to schistosomiasis is similar to the idiopathic form, progressing to chronic kidney disease in about 60% of cases [70].

It is likely that tubular alterations also contribute to the progression of nephropathy and the development of chronic kidney disease. However, data on this topic are scarce and need to be further clarified. In Egypt, about 10% of patients on chronic hemodialysis have schistosomiasis as the cause of their kidney disease [45].

21.10 Conclusions

In addition to significant glomerular alterations, which are well documented, *Schistosomiasis mansoni* is also associated with tubular alterations such as deficits in urinary concentration and acidification. In most cases, these alterations are asymptomatic from the perspective of urinary changes. Additionally, the disease predominantly affects younger individuals, who are at risk of losing kidney function and could benefit from measures to delay the progression of kidney disease. These aspects reinforce the importance of conducting tests to assess kidney function in all cases of schistosomiasis mansoni, potentially including more specific tests, such as urinary concentration and acidification tests, as well as microalbuminuria and urinary MCP-1, which

seem to be useful biomarkers for the early detection of schistosomal nephropathy.

The investigation of subclinical alterations through serum and urinary tests may be useful for the early diagnosis of renal involvement in schistosomiasis and for the consequent prevention of kidney disease progression. Renal function alterations are asymptomatic in most cases, and patients may only develop symptoms once there is significant loss of kidney function.

21.11 Take-Home Message

(suggested strategies to improve kidney health care, based on sustainable development goals, in the context of climate change, with focus of low- and middle-income countries, with scarce resources)

- *Schistosomiasis mansoni* is associated with glomerular and renal tubular alterations and these alterations may present asymptomatically.
- The investigation of subclinical changes, through serum and urinary biomarkers, is important for the early diagnosis of renal involvement in schistosomiasis
- Early detection of renal involvement in schistosomiasis is essential to prevent the development of chronic kidney disease.

Acknowledgments To dear Fábio Rocha for his help in developing the figures used in the chapter.

References

1. Mahmoud AAF. Esquistossomose. In: Bennett JC, Plum F, editors. Cecil: Tratado de Medicina Interna. 20.ed. Rio de Janeiro: Guanabara-Koogan; 1997. p. 2127–32.
2. Ross AGP, Bartley PB, Sleigh AC, et al. Schistosomiasis. N Engl J Med. 2002;346:1212–20.
3. Chitsulo L, Loverde P, Engels D. Disease watch: Schistosomiasis. TDR Nat Rev Microbiol. 2004;2:12–3.
4. Maguire JH. Trematodes (Schistosomes and Other Flukes). In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas and Bennett's: principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010. p. 3595–605.
5. Molyneu DH, Hotez PJ, Fenwick A. "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. Plos Med. 2005;2:1064–70.
6. Vanderwerf MJ, De Valasl SJ, Brooker S, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Trop. 2003;86:125–39.
7. Steinmann P, Keiser J, Bos R, et al. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infect Dis. 2006;6:411–25.
8. Passos ADC, Amaral RS. Esquistossomose mansônica: aspectos epidemiológicos e de controle. Rev Soc Bras Med Trop. 1998;31:61–74.
9. Katz N, Peixoto SV. Análise crítica da estimativa do número de portadores de esquistossomose mansoni no Brasil. Rev Soc Bras Med Trop. 2000;33:303–8.
10. Resendes APC, Souza SR, Barbosa CS. Hospitalization and mortality from mansoni schistosomiasis in the State of Pernambuco, Brazil, 1992/2000. Cad Saúde Pública. 2005;21:1392–401.
11. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Guia de vigilância epidemiológica. 7.ed. Brasília, DF, 2010.
12. Ministério da Saúde. DATASUS. http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/esquistobr.def. Accessed 25 Mar 2024.
13. Santos MCS, Oliveira GL, Mingoti AS, et al. Effect of environmental factors in reducing the prevalence of schistosomiasis in schoolchildren: An analysis of three extensive national prevalence surveys in Brazil (1950–2018). PLoS Negl Trop Dis. 2023;17(7):e0010804.
14. Blanchard TJ. Schistosomiasis. Travel Med Infect Dis. 2004;2:5–11.
15. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Doenças infecciosas e parasitárias: guia de bolso. 5. ed. ampl. Brasília, 2005. Available from: www.saude.gov.br/svs. Accessed 8 Mar 2012
16. Martinelli R, Silveira MA, Rocha H. Glomerulonefrites associadas às doenças parasitárias. In: Barros RT (Org.). Glomerulopatias: patogenia, clínica e tratamento. São Paulo: Sarvier, 2006. p. 352–371.
17. Domingues ALC, Novais S. Esquistossomose mansônica. In: Filgueira NA (Org.). Condutas em clínica médica. Rio de Janeiro: Medsi, 2004. p. 659–669.
18. Coutinho HM, Acosta LP, Wu HW, et al. Th2 cytokines are associated with persistent hepatic fibrosis in human Schistosoma japonicum infection. J Infect Dis. 2007;195:288–95.
19. Cheever AW, Hoffmann KF, Wynn TA. Immunopathology of schistosomiasis mansoni in mice and men. Immunol Today. 2000;21:465–6.

20. Corachan M. Schistosomiasis and international travel. Clin Infect Dis. 2002;35:446–50.
21. Mountford AP. Immunological aspects of schistosomiasis. Parasite Immunol. 2005;27:243–6.
22. Bina JC. Influência da terapêutica específica na evolução da esquistossomose mansoni. Rev Patol Trop. 1981;10:221–67.
23. Stephenson L. The impact of schistosomiasis on human nutrition. Parasitology. 1993;107:107–23.
24. Lamyman MJ, Noble DJ, Narang S, Dehalvi N. Small bowel obstruction secondary to intestinal schistosomiasis. Trans R Soc Trop Med Hyg. 2006;100:885–7.
25. Domingues ALC, Domingues LAW. Forma intestinal, hepatointestinal e hepatoesplênica. In: Malta J. Esquistossomose mansônica. Recife: Ed. UFPE, 1994. v. 5, p. 91–105.
26. Lambertucci JR, Serufo JC, Gerspacher-Lara R, et al. Schistosoma mansoni: assessment of morbidity before and after control. Acta Trop. 2000;77:101–9.
27. Andrade ZA, Van Marck EAE. Schistosomal glomerular disease. Mem Inst Oswaldo Cruz. 1984;79:499–506.
28. Prata A. Esquistossomose mansoni. In: Veronesi R, Foccacia R, editors. Tratado de Infectologia. São Paulo: Atheneu; 1997. p. 1354–72.
29. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa de Controle da Esquistossomose. Brasília, DF, 2006.
30. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Vigilância da Esquistossomose Mansoni: diretrizes técnicas/Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis.—4. ed.—Brasília: Ministério da Saúde, 2014. 144p. : il.
31. Fasogbon IV, Aja PM, Ondari EM, et al. UCP-LF and other assay methods for schistosome circulating anodic antigen between 1978 and 2022. Biol Methods Protoc. 2023;38(1):bpad006.
32. Barsoum RS. Schistosomal glomerulopathies. Kidney Int. 1993;44:1–12.
33. Van Velthuysen MLF. Glomerulopathy associated with parasitic infections. Parasit Today. 1996;12:102–7.
34. Rodrigues VL, Otoni A, Voieta I, et al. Glomerulonephritis in schistosomiasis mansoni: a time to reappraise. Rev Soc Bras Med Trop. 2010;43:638–42.
35. Queiroz FP, Brito E, Martinelli R. Influence of regional factors in the distribution of the histologic patterns of glomerulopathies in the nephrotic syndrome. Nephron. 1975;14:466–70.
36. Dos Santos WLC, Sweet GMM, Azevêdo LG, et al. Current distribution pattern of biopsy-proven glomerular disease in Salvador, Brazil, 40 years after an initial assessment. Braz J Nephrol. 2017;39(4):376–83.
37. Melo ME, Silveira MA, Martinelli R. Alterações renais nas doenças parasitárias: esquistossomose, leptospirose e malária. In: Barros E (Org.). Nefrologia: rotinas, diagnóstico e tratamento. Porto Alegre: Artmed, 2006. p. 309–316.
38. Deelder AM, Kornelis D, Marck V, et al. Schistosoma mansoni: characterization of two circulating polysaceharide antigens and the immunological response to these antigens in the mouse, hamster, and human infection. Exp. Parasitol. 1980;50:16–32.
39. Van Marck EA, Deelder AM, Gigase PL. Effect of parcial vein ligation on immune glomerular deposits in Schistosomamansoni infected mice. Br J Exp Pathol. 1977;58:412–7.
40. De Water R, Van Marck EA, Fransen JA, et al. Schistosoma mansoni: ultrastructural localization of the circulating anodic antigen and the circulating cathodic antigen in the mouse kidney glomerulus. Am J Trop Med Hyg. 1988;38:118–24.
41. Barsoum RS. Schistosomal glomerulopathy: selection factors. Nephrol Dial Transplant. 1987;2:488–97.
42. De Brito T, Carneiro CR, Nakhle MC, et al. Localization by immunoelectron microscopy of Schistosoma mansoni antigens in the glomerulus of the hamster (Mesocricetusauratus). Kidney Exp Nephrol. 1998;6:368–76.
43. Digeon M, Droz D, Noel LH, et al. The role of circulating immune complexes in the glomerular disease of experimental hepatosplenic schistosomiasis. Clin Exp Immunol. 1979;35:329–37.
44. Sobh M, Moustafa F, Ramzy R, et al. Schistosoma mansoni nephropathy in Syrian golden hamsters: effect of dose and duration of infection. Nephron. 1991;59:121–30.
45. Barsoum R. The changing face of schistosomal glomerulopathy. Kidney Int. 2004;66:2472–84.
46. Araújo SA, Neves PDMM, Wanderley DC, et al. The immunohistological profile of membranous nephropathy associated with chronic Schistosoma mansoni infection reveals a glomerulopathy with primary features. Kidney Int. 2019;96:793–4.
47. Brito T. Schistosoma mansoni associated glomerulopathy. Rev Inst Med Trop. 1999;41:269–72.
48. Nussenzveig I, De Brito T, Carneiro CR, et al. Human Schistosomamansoni-associated glomerulopathy in Brazil. Nephrol Dial Transplant. 2002;17:4–7.
49. Abensur H, Nussenzveig I, Saldanha LB, et al. Nephrotic syndrome associated with hepatointestinal schistosomiasis. Rev Inst Med Trop Sao Paulo. 1992;34:273–6.
50. Dos Santos WLC, Sweet GMM, Bahiense-Oliveira M, et al. Schistosomal glomerulopathy and changes in the distribution of histological patterns of glomerular diseases in Bahia, Brazil. Mem Inst Oswaldo Cruz. 2011;106:901–4.
51. Neves PDMM, Jorge LB, Cavalcante LB, et al. Schistosomiasis-associated glomerulopathy: Clinical aspects, pathological characteristics, and renal outcomes. Clin Nephrol. 2020;93:251–61.
52. Andrade ZA, Rocha H. Schistosomal glomerulopathy. Kidney Int. 1979;16:23–9.
53. Martinelli R, Rocha H. Revisão/Atualização em Nefrologia Clínica: Envolvimento glomerular

na esquistossomose mansônica. J Bras Nefrol. 1996;18:279–82.
54. Silva Júnior GB, Duarte DB, Barros EJG, et al. Schistosomiasis-associated kidney disease: a review. Asian Pac J Trop Dis. 2013;3:79–84.
55. Martinelli R, Brito E, Rocha H. Value of beta 1C/1A globulin serum levels as an early index of glomerular involvement in Schistosoma mansoni infection. Am J Trop Med Hyg. 1980;29:882–995.
56. Duarte DB, Vanderlei LA, Bispo RKV, et al. Renal function in hepatosplenic schistosomiasis—an assessment of renal tubular disorders. Plos One. 2014;9:1–15.
57. Sobh M, Moustafa F, El-Arbagy, et al. Nephropathy in asymptomatic patients with active Schistosoma mansoni infection. Inter Urol Nephr. 1990;22:37–43.
58. Hanemann ALP, Libório AB, Daher EF, et al. Monocyte Chemotactic Protein-1 (MCP-1) in patients with chronic schistosomiasis mansoni: evidences of subclinical renal inflammation. Plos One. 2013;8:1–5.
59. Martinelli R, Noblat ACB, Brito E, et al. Schistosoma mansoni-induced mesangiocapillary glomerulonephrites: influence of therapy. Kidney Int. 1989;35:1227–33.
60. Lima Verde EM, Lima Verde FAA, Silva Júnior GB, et al. Evaluation of renal function in human visceral leishmaniasis (kala-azar): a prospective study on 50 patients from Brazil. J Nephrol. 2007;20:432–8.
61. Oliveira RA, Silva Júnior GB, Souza CJ, et al. Evaluation of renal function in leprosy: a study of 59 consecutive patients. Nephrol Dial Transplant. 2008;23:256–62.
62. Oliveira RA, Lima CG, Mota RMS, et al. Renal function evaluation in patients with American Cutaneous Leishmaniasis after specific treatment with pentavalent antimonial. BMC Nephrol. 2012;13:44–9.
63. Duarte DB, Meneses GC, Lima DB, et al. Aquaporin-2 and NKCC2 expression pattern in patients with hepatosplenic schistosomiasis. Trop Med Int Health. 2020;25:1140–4.
64. Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, editor. The liver and portal hypertension. Philadelphia: Saunders; 1964. p. 50–64.
65. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–70.
66. Duarte DB, Vanderlei LA, Bispo RKV, et al. Acute kidney injury in schistosomiasis: a retrospective cohort of 60 patients in Brazil. J Parasitol. 2015;101:244–7.
67. Jiang Y, Beller DI, Frendl G, et al. Monocyte chemoattractant protein-1 regulates adhesion molecule expression and cytokine production in human monocytes. J Immunol. 1992;148:2423–8.
68. Segerer S, Nelson PJ, Schlöndorff D. Chemokines, chemokine receptors, and renal disease: from basic science to pathophysiologic and therapeutic studies. J Am Soc Nephrol. 2000;11:152–76.
69. Gryseels B, Polman K, Clerinx J, et al. Human schistosomiasis. Lancet. 2006;368:1106–18.
70. Martinelli R, Pereira JLC, Brito E, et al. Clinical course of focal segmental glomerulosclerosis associated with hepatosplenic Schistosomiais mansoni. Nephron. 1995;69:131–4.

Lymphatic Filariasis Nephropathy

22

Maria Eliete Pinheiro, Daniella Bezerra Duarte, Michelle Jacintha Cavalcante Oliveira, and Gilberto Fontes

22.1 Introduction

Lymphatic filariasis (LF), also popularly known as elephantiasis in one of its manifestations in the chronic and symptomatic phase, is an infectious disease caused by Nematoda helminths of the species *Wuchereria bancrofti, Brugia malayi*, and *Brugia timori*. *W. bancrofti* is the only etiological agent of LF in Africa and the Americas, *B. malayi* causes the disease in South and Southeast Asia and the Eastern Pacific, and *B. timori* in eastern Indonesia and the island of Timor. Humans are the only vertebrate hosts of *W. bancrofti,* and LF is considered an anthroponosis.

LF is a neglected tropical disease that is highly debilitating and causes severe functional disability and deformity in affected patients, with serious economic and social impacts [1]. In recent years, there has been a significant decrease in the number of LF cases worldwide due to the implementation of a control program by the World Health Organization, aiming to eliminate global transmission of the disease by 2030. However, the disease still affects thousands of people worldwide, with approximately 2/3 of infected individuals located in Asia. In Brazil, LF transmission has been significantly reduced in recent decades, presenting a focal nature, with special attention being paid to the city of Recife and its metropolitan region in Olinda, Jaboatão dos Guararapes, and Paulista. Other cities that were considered active foci, such as Belém do Pará (North region) and Maceió (Northeast region), are currently considered eliminated foci, according to the latest data from the Ministry of Health [2, 3].

The clinical presentation of FL is variable and may be asymptomatic or present acute manifestations (adenolymphangitis, dermatolymphangioadenitis, filarial fever, orchitis, orchiepididymitis) and chronic manifestations (lymphedema, hydrocele, chyluria, and elephantiasis) [4]. The severity of manifestations increases with age, and chronic lesions such as elephantiasis can become irreversible, causing disability and exposing their carriers to social prejudice. Tropical pulmonary eosinophilia (TPE) is a syndrome due to the patient's hyperimmune response to filarial antigens and is a relatively rare manifestation.

Studies show that LF can cause glomerular lesions, one of the characteristics of which is the deposition of immune complexes, but it can also present tubulointerstitial involvement [5, 6].

M. E. Pinheiro (✉) · D. B. Duarte · M. J. C. Oliveira
School of Medicine, Federal University of Alagoas, Maceió, Alagoas, Brazil

G. Fontes
Health Sciences Center, Federal University of São João del-Rei, São João del-Rei, Minas Gerais, Brazil
e-mail: gfontes@ufsj.edu.br

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_22

There are reports of persistent proteinuria in some cases, despite specific treatment of LF, requiring a greater understanding of renal involvement in this disease [7].

22.2 Epidemiology

It is estimated that there are approximately 120 million people worldwide infected with parasites that cause LF in tropical and subtropical areas. Of those infected, approximately 112 million are carriers of *W. bancrofti* and eight million are infected with *B. malayi* or *B. timori*. Of these, it is believed that approximately 25 million men present genital involvement, especially hydrocele, and 15 million women present with lymphedema in the lower limb [8].

According to the World Health Organization (WHO), LF affects 72 countries, and the main endemic areas are in Asia, Africa, and the western Pacific islands. LF caused by *W. bancrofti* occurs in sub-Saharan Africa, Southeast Asia, the Indian subcontinent, some Pacific islands, and focal areas in Latin America (Brazil, Dominican Republic, Guyana, and Haiti). It is estimated that there are approximately 12.6 million individuals at risk of LF infection in the Americas, 80% of whom are in Haiti [4]. LF caused by *Brugia timori* occurs in Timor Island and eastern Indonesia, and *B. malayi* causes the disease in South and Southeast Asia and the Eastern Pacific [3].

In Brazil, LF was probably introduced through the slave trade [9]. Until 1950, little was known about the distribution of LF in the country, and the first studies to map the distribution of the disease in the national territory were initiated in 1951. Between 1951 and 1958, several hemoscopic and entomological surveys were carried out, confirming the autochthonous transmission of LF in Brazil in some cities of Santa Catarina, Rio Grande do Sul, Pernambuco, Bahia, Maranhão, Alagoas, Pará, and Amazonas [10, 11]. From then on, actions to combat LF were implemented in these regions of Brazil, with a significant and progressive reduction in microfilaremia rates due to the treatment of parasitized individuals, with active foci remaining in Recife (PE) and Belém (PA) in recent decades [12]. Fontes et al. published a study in 1996 demonstrating the presence of an active focus of LF transmission in the city of Maceió (AL) [10]. In 2000, the WHO launched a program to eliminate LF worldwide, and Brazil has always been a partner in this proposal, having presented very favorable results and being close to the goal of eliminating transmission. The last active foci in the country were part of the city of Recife and some foci in the metropolitan region in an advanced elimination process. Maceió (AL) and Belém (PA) were active foci until a few years ago; however, the interruption of transmission in these locations has been demonstrated [2]. After decades of studies and programs for treatment, elimination, control, and surveillance in former endemic areas, Brazil is close to obtaining certification of the elimination of LF transmission in its territory. In early 2024, the Federal Government submitted the dossier to the World Health Organization for analysis to officially obtain this certification.

22.3 Evolutionary Cycle

Humans are the only vertebrate hosts of *W. bancrofti*, which is an important factor in the elimination process of LF [4]. In endemic areas, children are generally affected before the age of five and the prevalence of microfilaremia increases, mainly affecting individuals between the third and fourth decades [4, 13].

The vector mosquito of the causal agent of LF can be of several genera depending on the affected region. Among the main ones is *Culex,* with the species *C. quinquefasciatus* in Brazil, also common in other tropical and subtropical regions, being fundamental in the transmission of LF by *W. bancrofti. In addition to this, Anopheles, Aedes, Mansonia*, and *Coquillettidia* are also important. The vectors for *Brugia* are of the genera *Mansonia and Aedes* [4, 14]. Only the females of these insects are hematophagous and consequently involved in the transmission of the parasite.

The evolutionary forms that parasitize human hosts are adult worms (male and female) and embryos called microfilariae. The larval stages are found in the vector mosquito. Adult worms live for around 10 years in human lymph nodes and vessels. They are threadlike and have a thin, milky-white body. Males measure around 4 cm in length and 0.1 mm in diameter, and females measure 7–10 cm in length and 0.3 mm in diameter. Microfilariae, eliminated by pregnant females in the lymphatic ducts, enter the host's bloodstream, where they move actively. These forms have a flexible covering sheath and measure 280–300 microns in length. Observation of the sheath is important, since microfilariae of other filariid species, also found in the blood, do not have this structure, which is one of the morphological criteria for specific diagnosis.

In the insect vector, the microfilariae ingested during the blood meal in the human host transform into larvae and undergo 3 molts, transforming into infective larvae or L3. The life cycle of the parasite in LF begins with the introduction of these infective larvae into the human being during the bite of the infected vector. The larvae are deposited in the damaged skin of the healthy individual and, through active movements, through a break in the skin, reach the lymphatic vessels, where they undergo two molts, transforming into adult worms, which release microfilariae. The latter reach the bloodstream, where they can be sucked by the insect vector, restarting the cycle [2].

A characteristic of W. *bancrofti, observed in most* endemic regions, is the nocturnal periodicity of microfilariae in the peripheral blood of the human host: during the day, these forms are in the deep capillaries, mainly in the lungs, and during the night, they appear in the peripheral blood [2]. The peak of microfilaremia occurs between 10:00 p.m. and midnight, coinciding, in most endemic regions, with the preferred time of hematophagy of the main transmitting insect, C. *quinquefasciatus* [2]. From the end of the night onwards, microfilariae are found in very small numbers or are not detected during the day in the peripheral blood. In the South Pacific, *W. bancrofti* microfilariae do not present this characteristic, being subperiodic and with a peak of microfilaremia occurring around 3:00 pm [4].

22.4 Clinical Manifestations

LF can present itself in different clinical forms, from the absence of symptoms to acute and chronic manifestations. In a didactic manner, after the penetration of the infective larva, the sequence of events is as follows: prepatent period (entry of infective larvae until the appearance of microfilaremia—approximately 7–9 months), asymptomatic microfilaremia, and acute and chronic filariasis. Usually, the professional does not detect all these phases [15, 16].

The clinical presentation in individuals living in endemic areas depends on numerous factors, including the host's immune response, age at first exposure, species involved, intensity of exposure to infected mosquitoes, prenatal sensitization, and other unknown factors [4, 17].

The initial infection provokes a Th2 immune response with consequent production of cytokines, including IL-5, resulting in high levels of IgE and IgG4. With the late progression of the infection, T lymphocyte suppression occurs, compromising the production of Th1 and Th2 cytokines, contributing to the chronicity of the disease [4, 18].

Acute manifestations of LF, especially caused by *W. bancrofti*, a species of interest in Brazil, are characterized by attacks of adenolymphangitis associated with fever and malaise. In men, adenolymphangitis may be in the genitals, presenting as acute orchiepididymitis. Inflammatory nodules in the breasts, scrotum, and subcutaneous tissue are acute manifestations of filariasis. The manifestations are characterized by local edema, hyperemia, and a sensation of soreness or pain that is sometimes very intense, especially in the genital region. These episodes, which are short-lived, resolve spontaneously in most cases. The presence of microfilariae may be present in approximately 50–60% of cases. The inflammatory symptoms are basically caused by the death of the adult worm, either "spontaneously" or by antifilarial treatment. Since the acute episode is

caused by the death of the worm, antifilarial treatment is not indicated at this stage of the disease, except when microfilaremia persists [15, 16, 19].

Filarial fever is acute, with self-limiting episodes in the absence of lymphangitis or lymphadenopathy and can be confused with other causes of fever in tropical regions, such as malaria [4]. Tropical pulmonary eosinophilia (TPE) is another manifestation and can be caused by host hyperresponsiveness to microfilariae in the lungs. It is rare in patients under 15 years of age and affects a small proportion of individuals infected with *W. bancrofti* and *Brugia*. It presents with asthma-like attacks, paroxysmal cough, predominantly nocturnal, anorexia, and weight loss, presenting peripheral eosinophilia, and, in general, no microfilariae are found in the peripheral circulation. For this reason, this clinical picture is also known as "occult filariasis" [15].

Chronic manifestations are especially important due to the limiting and stigmatizing nature they impose on the patient. The clinical presentation will depend on the location of the lymphatic damage. The best known is lymphedema, which initially presents as soft tissue and progresses to hard and extensive edema, mainly in the lower limbs (Fig. 22.1). Other important chronic manifestations are unilateral or bilateral hydrocele (Fig. 22.2) and chyluria [7].

Chyluria consists of the loss of lymph through the urine due to increased pressure in the obstructed lymphatic system, caused by the retrograde flow of chyle through the renal lymphatics, which become varicose and eventually rupture into the urinary tract [51]. This loss of lymph may be sporadic, especially when eating fatty foods. Patients usually complain of fatigue and weight loss resulting from significant protein losses through the urine. Due to the decreased immune defense caused by the loss of lymph, these patients are more prone to infections. Anemia may be found in cases of hematochyluria [16, 19]. The diagnosis of chyluria of filarial origin should be made after ruling out other causes, such as trauma, pregnancy, and tumors, except when microfilariae are found in the urine [20].

Fig. 22.1 Lymphatic edema (elephantiasis) in the lower limb. (Photo kindly provided by Dr. Giberto Fontes/Dra. Eliana MM da Rocha)

Fig. 22.2 Hydrocele. (Photo kindly provided by Dr. Giberto Fontes/Dra. Eliana MM da Rocha)

In patients with elephantiasis, microfilaremia is generally absent. In chyluria, it may be present in 50% of cases. In cases of hydrocele, microfilariae may be found in the fluid of the scrotum and, in some cases, in the bloodstream.

22.5 Diagnosis

LF should always be considered in endemic areas in patients presenting with any of the acute or chronic symptoms. Diagnosis is based on specific findings described below and may be aided by nonspecific laboratory findings, such as eosin-

ophilia, increased serum IgE, microscopic hematuria, and proteinuria.

The specific diagnosis is established by the detection of *W. bancrofti filarial antigen*, demonstration of microfilaria or parasite DNA in peripheral blood, or by the presence of the adult worm in the lymphatic system. Finding the adult worm in biopsy material is rarer, but it can occur [21].

The detection of circulating antigen has the advantage of being performed with blood collected at any time of the day or night and even in amicrofilaremic individuals [2, 4, 21]. The investigation of circulating antigens of the parasite can be performed using the rapid immunochromatography technique (ICT *card test*) or through the ELISA immunoenzymatic technique [2]. Currently, the FTS (filariasis test strip) immunochromatographic test is used, which detects filarial antigen in blood collected by finger prick at any time. This test is independent of the concentration of microfilariae and has good sensitivity and specificity and can be used for mapping, monitoring and evaluating the transmission of LF in epidemiological studies.

Microfilariae testing in blood samples can be performed using a thick smear (approximately 20–100 microliters of blood) [2, 22]. To test for microfilariae, blood should be collected at night, due to their nocturnal periodicity in the host's peripheral blood [2]. To test for microfilariae, blood filtration through polycarbonate membranes can also be performed, using larger volumes of blood, increasing the sensitivity of the test [2]. This technique is used to monitor post-treatment cure. Other diagnostic options include polymerase chain reactions (PCR) to test for parasite DNA and ultrasound to test for adult worms in the lymphatic system [2].

22.6 Treatment

The treatment of LF is based on the action of the drug on the parasite and the possibility of coinfection with *Onchocerca volvulus* and *Loa loa* [4] must also be considered.

In 1997, the World Health Assembly set 2020 as the target year for the elimination of LF as a global public health problem. Since then, the WHO has been working to achieve this goal. In 1997, Brazil joined the call of the WHO and the World Health Assembly by becoming a signatory to this proposal. Despite the progress made in eliminating LF as a global public health problem, the established target has not been achieved in some of the endemic areas of the world, and thus the WHO established 2030 as the new target year for the global elimination of LF [23].

The "Global Programme for the Elimination of Lymphatic Filariasis" (GPELF) launched in 2000 by WHO was based on two main components: (i) mass drug administration (MDA) to interrupt transmission, and (ii) morbidity management and disability prevention (MMDP) to support those already affected by chronic manifestations of LF [1, 24]. The following targets were added to this agenda by 2030: endemic countries must have completed their mass treatment programmes (MDA); they must have implemented post-MDA or post-validation surveillance; and they must effectively have a minimum package of care for those with LF morbidity [23].

The GPELF recommends the massive administration of a single-dose combination of drugs provided annually to eligible individuals in LF-endemic areas. The combination consists of: diethylcarbamazine (DEC) + albendazole in countries not endemic for onchocerciasis and ivermectin+albendazole in cases of onchocerciasis-endemic countries with adherence of more than 65% of the population of the area [24].

Recently, a study based on mathematical models demonstrated that the combined annual administration of three drugs (ivermectin, DEC and albendazole) could accelerate the elimination of LF by 1–2 years in areas of low prevalence and by 4–5 years in areas of moderate and high prevalence [25, 26]. Thus, the World Health Organization recommended, as of 2017, the use of combination therapy with three drugs (ivermectin + DEC + albendazole) in the case of endemic areas, without coinfection (*O. volvulus* or *L. loa*) that did not start previous treatment with two drugs or that had less than four effective cycles of treatment and in places where there is

still evidence of transmission despite previous treatment [27].

In Brazil, from 2003 onward, research was implemented to evaluate the elimination of LF transmission in the metropolitan region of Recife, using mass treatment, a decisive step in defining the current situation of this disease in the country and new control and surveillance strategies [28].

Treatment of LF is indicated for all individuals with active infection, regardless of whether they present clinical manifestations related to the presence of the parasite. The drug of choice for individual treatment is diethylcarbamazine citrate (DEC), with the WHO recommended therapeutic regimen being 6 mg/kg of body weight/day, orally, for 12 days [2]. This treatment may be repeated several times, if necessary, until the blood microfilariae disappear. During treatment, especially in the first 3 days, the patient may present adverse reactions due to the disintegration of the parasites, such as fever, headache, body and joint pain, malaise, transient hematuria, and local reactions, such as lymphangitis, funiculitis, and orchitis. All these manifestations tend to disappear spontaneously, and it is not necessary to interrupt treatment. The drug leads to a rapid and marked disappearance of microfilariae from the bloodstream, and the effect is observed within the first hours after the start of treatment. DEC also has considerable action on adult worms, and indirect evidence of this action is the disappearance of microfilariae after treatment. DEC is also the drug of choice for cases of EPT, in which marked clinical improvement occurs a few days after the start of treatment and lung function returns to normal if the damage to the organ was not extensive. In the case of EPT, treatment should be extended for up to 30 days. The use of DEC significantly reduces acute symptoms and reduces the development of lymphatic lesions in the early stages, but patients with severe hydrocele or elephantiasis do not show improvement after treatment.

Fig. 22.3 Bottle on the left with milky urine (chyluria) and bottle on the right with normal urine. (Photo kindly provided by Dr. Maria Eliete Pinheiro)

22.7 Renal Involvement

Renal involvement in LF may occur, among other presentations, in the form of chyluria, due to the presence of lymph in the renal pelvis, coming from the intestine. The appearance of the urine then becomes milky [29] (Fig. 22.3).

Hematochyluria is a known complication of LF; however, chyluric hematuria, although rare, has also been reported in this pathology [30–33]. Unlike what occurs with chyluria, the cause of isolated hematuria has not yet been clarified. Among the possible mechanisms considered most likely are the rupture of small blood vessels into the dilated lymphatic capillaries or diapedesis of blood corpuscles into the lymphatic channels [31].

Other forms of renal involvement associated with filariasis have been documented in the literature. In recent years, cases of membranous glomerulonephritis [34, 35]; recurrent hematuria [30–32]; acute eosinophilic glomerulonephritis [36]; glomerulonephritis with the presence of IgG, IgM, and C_3 deposits [37]; mesangioproliferative glomerulonephritis [38–40]; and immune complex glomerulonephritis in patients with chy-

luria [39] have been described and membranoproliferative glomerulonephritis [41].

A previous study of 50 patients with membranoproliferative glomerulonephritis (MPGN) in India found bancroftian filariasis as an associated disease and possible source of chronic antigenemia in three (6%) of these individuals. The renal histological alterations were subendothelial deposits, with or without mesangial deposits, and eosinophilia and hypocomplementemia occurred in 88% of all patients (Type 1 MPGN). The clinical and laboratory findings in the 50 patients, except for eosinophilia, were like those of other studies of MPGN. On the other hand, the prevalence of type 2 MPGN was rarer than in most reports from Western developed countries, which could be explained by the known association of type 1 MPGN with chronic antigenemia conditions common in the tropics [41]. This was the first report of bancroftian filariasis associated with MPGN, although association with other histological types had been previously described [36, 38].

Renal alterations associated with another filarial species, *Loa loa*, have been described, where asymptomatic proteinuria was the main clinical presentation, discrete microscopic hematuria occurred frequently and occasionally microfilariae (usually dead) could be seen in the urinary sediment. The few cases that included renal biopsy showed pathological alterations described as "chronic glomerulonephritis," "edema of some or all of the capillary walls, occasionally with endothelial proliferation," or "infiltration of the renal interstitium with mononuclear cells" [42]. Membranous glomerulopathy has also been reported in *Loa loa* infestation [35].

A previous study observed renal alterations in 45% of 20 untreated asymptomatic microfilaremic patients. In this study, the presence of hematuria and/or proteinuria was evidenced. Because the patients were microfilaremic, the possibility of microfilariae playing a mechanical role in the genesis of renal damage was suggested. Microfilariae could reach the renal tubule by passing through the glomerular capillaries or by rupture of renal lymphatics [31, 43]. However, as microfilaruria was not detected in these patients, the hypothesis was raised that renal injury was secondary to the formation of antigen-antibody complexes initiated by parasitemia [43]. Other authors have suggested that renal injury, although rare, may occur due to the host's immune response through the deposition of immune complexes (ICs) [36, 37, 39, 41, 44].

Regarding the action of circulating ICs detected by some authors in this type of patient [39, 45–48], in only one study, in patients with onchocerciasis, the presence of filarial antigen was associated with abnormalities in renal biopsies [49]. Similar findings were produced experimentally in animal models of *O. volvulus*, through optical microscopy, finding thickening of the glomerular basement membrane (GBM), dense subendothelial deposits, and in the GBM, which were associated with high and prolonged microfilaremia. The subendothelial deposits may correspond to Ag-Ab complexes described in other diseases. However, the morphology and distribution of these deposits, equally distributed along the glomerular capillary, differ from those usually associated with the deposition of ICs, which form electron-dense deposits randomly located along the GBM, subepithelial, intramembranous, or subendothelial areas of the glomerular capillary wall. The exact nature of the lesions described is unknown to date, although they may be induced by Ags of the microfilaria and/or adult worm [50].

The mechanism of deposition of the circulating ICs detected in Bancroftian filariasis remains speculative. Although there is ample evidence of the presence of these circulating ICs, little is known about the characterization of the antigen in the IC [44]. In addition, other parasitic infections are present in areas where filariasis is endemic, and other Ags from these infections can also induce circulating ICs. However, it has been demonstrated that ICs can modulate the immune response, and it is known that immunomodulation is a primary finding of filarial infection. In addition, the pathogenic capacity of ICs is well known, and several of the filarial-induced manifestations are compatible with an etiology mediated by them [44, 47].

An important contribution to the understanding of this problem was made in a study that evaluated the effect of therapy with the drug Diethylcarbamazine (DEC) on microfilaremia and the immune status of 27 carriers of *Wuchereria bancrofti* for two years. Persistence of microfilaremia was observed in four of the 27 cases after DEC therapy. These patients were treated again, and microfilaremia became negative on day 60. Additionally, there was a gradual decrease in the mean titers of IgM and IgG filarial antibodies (Abs) and a significant increase in microfilarial antigen (mfAg) levels on day 7, followed by a gradual decrease in these levels, reaching levels lower than pretreatment levels on day 60. Filarial immune complexes (ICs) were also present in all samples, showing circulating ICs on day 7, which must be related to the decrease in IgM and IgG Abs in the circulation. Like Ags, IC levels also showed a decrease up to day 60. However, about 12 patients showed microfilaremia and antigenemia at day 360°, showing that DEC had only temporarily attenuated the effect of the adult worm [48].

Still in relation to this study, microfilarial Ag was found in the urine of 41% of patients before treatment and in all patients during treatment, correlating with the administration of DEC and with the elevation of Ags and ICs in blood. These results indicate that the detection of Ag in urine may be useful as a marker to determine whether the patient took the drug in filarial control programs [48].

Of all the parameters studied, the detection of microfilarial Ag was considered the most promising indicator of infection, even when microfilariae were not detected in peripheral blood [48]. Corroborating this statement, another author observed that although microfilaremia levels fell drastically after treatment, mf Ag and IgG Ab titers were increased 1 month after treatment and, despite showing a progressive decrease, were present 1 year later, with and without residual microfilaremia [51]. These results suggest that DEC has partial macrofilaricidal activity against *W. bancrofti*, at least at the dosage recommended by the WHO for the microfilaremia phase. The impressive reduction of microfilariae after treatment, despite the significant persistence of antigenemia, can therefore be explained by the sublethal effect of the drug on adult worms. Therefore, these findings suggest that the detection of parasitic Ag represented a valuable contribution to monitoring the efficacy of the therapy [48, 51].

The evaluation of the efficacy of DEC on the adult parasite "in vivo," through the observation of "nests" of these worms that were detected in the scrotal area by ultrasonography, showed that a significant proportion of them were not susceptible to DEC during the study period [52]. This observation corroborates the previous findings of only partial macrofilaricidal activity.

Another important renal alteration found in filariasis was the presence of proteinuria, significantly higher than in the control group, observed in an epidemiological study of 1011 patients, carried out in an endemic region for onchocerciasis. In a second phase of the study, a more detailed investigation was performed, including renal biopsies of 63 consecutive patients admitted to a referral hospital, with severe proteinuria and/or renal failure, from the onchocerciasis zone. There were a variety of possible causal factors for nephropathy, but in 9 cases, filarial antigen was demonstrated in immune complex deposits in the kidney. Although there were multiple coexisting parasitic infections, it was not believed that this was the cause of the higher frequency of nephropathy in this group, because most of these parasites are intestinal parasites that do not cause renal alterations. The major difference between the two populations with respect to their antigen reservoir was the presence of O. *volvulus* in most of the group, with a higher prevalence of proteinuria [49].

In another study, proteinuria was found in various stages of lymphatic filariasis in patients infected with *Brugia malayi*. The study consisted of evaluating groups of patients in three different phases of the disease: normal endemic individuals with high levels of specific Ab and non-endemic controls. The filariasis carriers were distributed as follows: 1—asymptomatic microfilaremic individuals; 2—patients with acute manifestations, and 3—patients with chronic

manifestations. Several patients underwent treatment with DEC. Quantitative proteinuria was investigated, and complementary tests were performed to discriminate between tubular or glomerular lesions. Serum IgG rheumatoid factor was also determined. Neither the normal endemic individuals nor the controls had evidence of renal alterations, whereas the patients with filarial infection presented significantly elevated proteinuria when compared to the control group. There was no significant difference between the three groups of infected individuals, although proteinuria levels were higher in cases of chronic disease, predominantly affecting the glomerulus, and lower in asymptomatic microfilaremic individuals, with characteristics of tubular injury. Treatment with DEC did not significantly alter the degree or characteristics of proteinuria, but relatively high levels of microalbuminuria in the urine of treated individuals suggested glomerular alterations in these cases. IgG rheumatoid factor did not appear to play a role in filarial infection associated with renal disease. In conclusion, proteinuria appears to be a common event in *Brugia malayi filariasis*, involving both tubular and glomerular compartments, and its pathogenesis is obviously complex [53].

Proteinuria may simply be a marker of the extent of glomerular damage or may itself promote subsequent disease progression to hyaline sclerosis [54]. Proteinuria increases in an experimental model of renal mass ablation—because of loss of glomerular barrier selectivity—soon after surgery and well before glomerulosclerosis develops [55]. The sustained increase in glomerular capillary flow and pressure in this model is eventually associated with glomerular injury, as documented by epithelial cell vacuolization and pedicel fusion [55]. Findings of near-normal glomerular epithelial cell structure and function in rats with remaining kidneys 3 weeks after renal ablation, when the animals are already proteinuric, suggest that proteinuria precedes the structural changes of glomerular epithelial cells detectable by electron microscopy [56].

In any case, proteinuria is recognized as a marker of kidney damage and may be transient or persistent. When it persists, the cause must be investigated. Persistent proteinuria is characterized by values above normal in repeated samples and may originate through three mechanisms: *glomerular alteration*, *tubular injury*, and *protein overload* [57, 58].

22.7.1 Proteinuria of Glomerular Origin:

It is the most commonly found type, related to primary pathological processes of the kidney itself or to systemic diseases. This type of proteinuria is predominantly made up of albumin and may present as the only sign of glomerular damage [57, 58]. If moderate molecular weight proteins (40,000–90,000 Da) such as albumin are present in the urine, the glomerular defect is called *selective*. On the other hand, if moderate and high molecular weight proteins are present in the urine, the proteinuria is called *nonselective* [58].

22.7.2 Tubular Proteinuria

It usually consists of proteinuria consisting of low molecular weight proteins, commonly resulting from alterations in tubular protein reabsorption capacity and frequently indicating the presence of tubular injury. Substances found in increased amounts in the urine in this type of proteinuria include β_β-microglobulin, RBP, lysozyme, α_β -glycoprotein, and several hormones and enzymes. Disorders associated with isolated tubular proteinuria usually result in less than 1 g of total urinary protein per day [57, 58].

22.7.3 Overload Proteinuria

It is caused by a nonrenal disorder, where excess low molecular weight proteins are filtered by the glomerulus, exceeding the reabsorptive capacity of the tubules. This type of proteinuria has the classic form of Bence-Jones proteinuria, found in multiple myeloma. However, other pathologies that occur with exogenous or endogenous eleva-

tion of plasma protein can give rise to this type of proteinuria [57, 58].

In certain situations, proteinuria may be found resulting from the sum of these three different mechanisms.

To assess proteinuria, it is necessary to differentiate its origin, whether glomerular or tubular. Tests for detecting albumin (the main protein in glomerular proteinuria) are readily available, but there are no simple tests for detecting light chain immunoglobulins and low molecular weight proteins, which predominate in overload and tubular proteinuria. These small proteins can be detected by more sophisticated tests, such as electrophoresis, chromatography, and immunoenzymatic methods [57, 58].

To determine renal disease in bancroftian filariasis, a study was conducted in the city of Maceió at a time when the city was considered an endemic area for the disease. Microfilaremic individuals were studied before (AT), during (DT), and after (PT) treatment with diethylcarbamazine (DEC) (6mg/kg/day, single oral dose, for 12 days) [7].

Ninety-six asymptomatic microfilaremic patients were evaluated, of which 23 underwent more detailed investigation. The patients were randomly selected, with 04 (17.4%) women and 19 (82.6%) men, aged 20 ± 8 (X ±SD) years. All individuals were clinically and laboratory evaluated AT, on the 5th and 11th days of DEC, under hospitalization. They were also evaluated at 1, 3, 6, 12, 18, and 24 months after treatment [7].

Diagnostic evaluation: urinalysis, 24-h proteinuria, microfilaremia, microfilaruria, creatinine, creatinine clearance, urea, microalbuminuria, retinol binding protein (RBP), C3 and C4, serum protein electrophoresis, complete blood count, and protoparasitological examination. Plain abdominal X-ray and renal and urinary tract ultrasonography were also performed in all patients, and renal biopsy in 10 of them [7].

A control group of 10 individuals, aged 25 ±2 years, underwent the same procedures, except for renal biopsy [7].

All patients were asymptomatic AT. AT microfilaremia was 10.9 ±15.8 (X ±DP) mf/20 μl, but

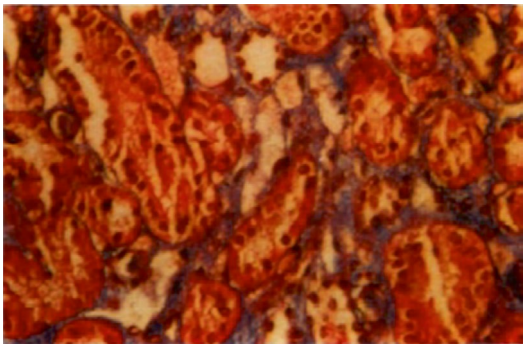


Fig. 22.4 Optical microscopy showing a small focus of tubular atrophy, surrounded by discrete fibrosis, stained with Masson's trichrome (400x magnification). (Photo kindly provided by Dr. Maria Eliete Pinheiro)

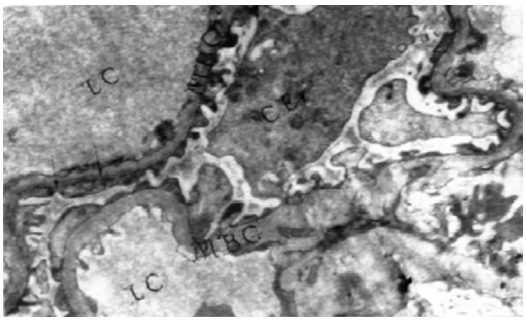


Fig. 22.5 Electron microscopy showing normal glomerular basement membrane, with arrows pointing to focal loss of pedicels (magnification 4,000x). (Photo kindly provided by Dr. Maria Eliete Pinheiro)

all patients tested negative 6 months later. Microfilaruria was positive in 01 patient. Renal function was normal in 100% of patients, persisting in this form PT. Transient hematuria was observed in 01 patient DT [7].

The control group showed normal renal function and proteinuria quantitatively at normal levels AT, DT, and PT in all cases. Differently, urinary protein excretion was 303.8 ± 168.7* (X ±DP) mg/24h AT; 335.9 ± 300.8* on the 5th; 280.4 ± 195.1* on the 11th day; and 304.9 ± 204.9*; 211.5 ± 114.3*; 142.8 ± 67.3; 325.3 ± 165.7; 302.3 ± 193.1*; 256.3 ± 156.6* mg/24h on the 1st, 12th, 18th, and 24th days, months of evaluation, respectively ($p < 0.05$ vs control group). Therefore, treatment with DEC

did not modify the proteinuria profile. RBP was normal in 20 individuals with proteinuria. Microalbuminuria was slightly increased and DT significantly increased, thus persisting PT [7].

As proteinuria persisted, renal biopsy was performed in 10 patients. The renal alterations found were mild focal tubular atrophy (Fig. 22.4), isolated glomerulosclerosis, and mild focal fusion of pedicels (Fig. 22.5). The study showed mild proteinuria, probably of glomerular origin, and the treatment did not alter its levels, which allowed us to infer the importance of this finding in areas endemic for filariasis [7].

22.8 Conclusions

Lymphatic filariasis is a neglected tropical disease that can cause significant morbidity to the individual affected by its chronic and disabling nature. The World Health Organization has been developing a Program to Eliminate the Transmission of Lymphatic Filariasis worldwide, with Brazil participating in this proposal, which aims to eliminate the disease by 2030.

Renal involvement in LF can occur in several ways, including chyluria, hematochyluria, and proteinuria. Membranous and membranoproliferative glomerulopathy have been described. According to a previous study, treatment with DEC does not appear to have modified proteinuria.

22.9 Take-Home Message

- Lymphatic filariasis (LF) is a debilitating neglected tropical disease caused by nematodes such as *Wuchereria bancrofti*.
- LF affects millions globally, with hotspots in Asia, Africa, the Pacific, and parts of Latin America, including historical foci in Brazil.
- LF symptoms range from asymptomatic to acute (fever, lymphangitis) and chronic (lymphedema, hydrocele, chyluria).
- Renal complications, such as glomerulonephritis and persistent proteinuria, are notable but underrecognized.
- Diethylcarbamazine (DEC) is the primary treatment, but it shows limited efficacy in addressing proteinuria and chronic complications.
- WHO targets LF eradication by 2030, focusing on mass drug administration and disability prevention.

Acknowledgments To Prof. Dr. Eliana Maria Mauricio da Rocha, Full Professor at the Federal University of São João Del Rei—UFSJ, who was responsible, together with Prof. Gilberto Fontes, for the study of FL in Maceió, until the elimination of transmission in this former focus in Brazil.

References

1. Global Program to Eliminate Lymphatic Filariasis: progress report, 2016. Wkly Epidemiol Rec 2017; 92:594.
2. Brazil. Ministry of Health. Health Surveillance Secretariat. Department of Epidemiological Surveillance. Guide to epidemiological surveillance and elimination of lymphatic filariasis/Ministry of Health, Health Surveillance Secretariat, Department of Epidemiological Surveillance. Brasília: Ministry of Health; 2009. 80p.: ill.—(Series A. Standards and Technical Manuals)
3. Neglected infectious diseases in the Americas. Success stories and innovation to reach the neediest. Washington, DC: PAHO; 2016.
4. Klion MD. Post TW, editor. Lymphatic filariasis: epidemiology, clinical manifestations and diagnosis. Waltham, MA: UpToDate. UpToDate Inc. http://www.uptodate.com. Accessed on 23 Mar 2018
5. Van Velthuysen ML, Florquin S. Glomerulophaty associated with parasitic infections. Clin Microbiol Rev. 2000;13(1):55–66.
6. Langhammer J, Birk HW, Zahner H. Renal disease in lymphatic filariasis: evidence for tubular and glomerular disorders at various stages of the infection. Trop Med Int Health. 1997;2(9):875–84.
7. Pinheiro ME. Renal evaluation of patients with bancroftian filariasis. Thesis (Doctorate in Medicine, Postgraduate in Nephrology). UNIFESP, São Paulo. 122pp, 1998.
8. World Health Organization. Lymphatic Filarials. http://www.who.int/lymphatic_filariasis/epidemiology/en/. Accessed in Mar 2018.
9. Orhiel TC. Filariae. In: Beaver PC, Jung RC, editors. Animal agents and vectors of human diasease. 5th ed. Philadelphia: Lea & Febriger; 1985. p. 171–91.
10. Fontes G. Epidemiological aspects of lymphatic filariasis caused by Wuchereria bancrofti in the State of Alagoas. Thesis (Doctorate in Sciences). UFMG. 179pp, 1996.

11. Rachou RG. Concept and program of prophylaxis of bancroftian filariasis in Brazil. Brazil J Malariol Tropic Dis. 1960;12(1):11–40.
12. MS (Ministry of Health). Control of endemic diseases in Brazil (from 1979 to 1984). Brasília (DF): Superintendence of Public Health Campaigns, SUCAM, 154p., 1985.
13. Witt C, Ottesen EA. Lymphatic filariasis: an infection of childhood. Trop Med Int Health. 2001;6:582.
14. WhiteGB. Studies on transmission of Bancroftian Filariasis in North-eastern Tanzania. Trans R Soc Trop Med Hyg. 1971;65:871–29.
15. Dreyer G, Dreyer P, Norões J. Bancroftian Filariasis. In: Lucena VG, editor. Clinical Service Doctor at the Hospital das Clínicas of UFPE. Conduct in medical clinic University Press; 2007. p. 641–8.
16. Dreyer G, Coutinho A, Albuquerque R. Clinical manifestations of bancroftian filariasis. Rev Assoc Med Bras. 1989;35:189–96.
17. Lymphatic Filariasis: Diagnosis and Pathogenesis. WHO expert committee on filariasis. Bull World Health Organ. 1993;71:3518.
18. Nutman TB, Kazura J. Lymphatic filariasis. In: Guerrant R, Walker DH, Weller PF, editors. Tropical infectious diseases: principles, pathogens and practice, vol. 20. 3rd ed. Philadelphia: Sauders Elsevier; 2011. p. 729.
19. World Health Organization. Lymphatic filariasis: the disease and its control. Expert committee on filariasis. Fifth report. Technical reports series, 821, 75pp, 1992
20. Kibukamusoke JW. Chyluria. In: Tropical nephrology. Australia, Citforge PTY. Ltd.; 1984. p. 360–8.
21. Kumar B, Karki S, Yadava SK. Role of fine needle aspiration cytology in diagnosis of filarial infestation. Diagn Cythopatol. 2011;39:8.
22. Dissanayake S, Rocha A, Noroes J. Evaluation of PCR-based methods for the diagnosis of infection in bancroftian filariasis. Trans R Soc Trop Med Hyg. 2000;94:526.
23. WHO. Ending the neglect to achieve the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2020. p. 196.
24. Guideline: Training in monitoring and epidemiological evaluation of intervention with collective treatments for the elimination of lymphatic filariasis: participant guide. Italy: World Health Organization, 2015.
25. Ndeffo-Mbah ML, Galvani AP. Global elimination of lymphatic filariasis. Published online December. 2016;21 https://doi.org/10.1016/S1473-3099(16)330544-8.
26. Irvine MA, Stolk WA, Smith ME, et al. Effectiveness of a triple-drug regimen for global elimination of lymphatic filariasis: a modeling study. Lancet Infect Dis, 2016. Published Online Dec 21, 2016. https://doi.org/10.1016/S1473-3099(16)30467-4
27. Guideline: Alternative mass drug administration regimens to eliminate lymphatic filariasis. Geneva: World Health Organization, 2017.
28. Rocha A, Santos EM, Oliveira P, Brandão E. History of lymphatic filariasis control actions in Olinda, Pernambuco, Brazil. Rev Patol Trop. 2016;45:339–48.
29. Franco-Paredes C, Hidron A, Steinberg J. A woman from British Guyana with recurrent back pain and fever. Chyluria associated with infection due to Wuchereria bancrofti. Clin Infect Dis. 2006;42:1297–340.
30. Dufour B, Lepage T. Une cause rare d'hématurie: la filariasis. J Urol Nephrol (Paris). 1978;84:231–5.
31. Mukherjee SK, Mukherjee AK, Sem JK. Filariasis with recurrent hematuria. JAMA. 1974;230(9):1254–5.
32. Nigam P, Sriwastava RP, Gupta, Sharma RS, Vajpayee GN. Haematuria in filariasis. Indian Med Assoc. 1979;62:249.
33. Sapico FL, Baltazar RF. Filariasis presenting as a case of gross hematuria. Acta Med Philipp. 1967;3(4):273–5.
34. Bariety J, Barbier M, Laigre MC, Tcherma G, Samareq P, Milliez P. Proteinurie et loase. Study histologique, optique et életronique d'un cas. Bull Soc Med Hop Paris. 1967;118:1015–25.
35. Pillay VKG, Kirch E, Kurtzman NA. Glomerulopathy associated with filarial loiasis. JAMA. 1973;225:179.
36. Date A, Gunasekaran V, Kirubakaran MG, Shastry JCM. Acute eosinophilic glomerulonephritis with Bancroftian filariasis. Postgrad Med J. 1979;55:905–7.
37. Waugh DA, Alexander JH, Ibels LS. Filarial chyluria associated glomerulonephritis and therapeutic considerations in the chyluric patient. Aust NJ Med. 1980;10:559–62.
38. Chugh KS, Singhai PC, Tewuri SC, Nath IVS, Datta EN. Acute glomerulonephritis associated with filariasis. Am J Trop Med Hyg. 1978;27(3):630–1.
39. Ormerod AD, Petersen J, Hussey JK, Weir J, Edward N. Immune complex glomerulonephritis and chronic anaerobic urinary infection-complications of filariasis. Postgrad Med J. 1983;59:730–3.
40. Yap HK, Woo KT, Yeo PPB, Chiang GSC, Singh M, Lim CH. The nephrotic syndrome associated with filariasis. Ann Academic Med. 1982;11(1):61–3.
41. Date A, Neela P, Shastry JCM. Membranoproliferative glomerulonephritis in a tropical environment. Ann Trop Med Parasitol. 1983;77(3):279–85.
42. Zuidema PJ. Renal changes in loiasis. Folia Med Neerl. 1971;14:168–72.
43. Dreyer G, Ottesen EA, Galdino E, Andrade L, Rocha A, Medeiros Z, Moura I, Casimiro I, Béliz F, Coutinho A. Renal abnormalities in microfilaraemic patients with Bancroftian Filariasis. Am J Trop Med Hyg. 1992;46(6):745–51.
44. Dissanayake S, Galahitiyawa SC, Ismail MM. Immune complexes in Wuchereria bancrofti infection in man. Bull World Health Organ. 1982;60(6):919–27.
45. Ganajana A, Bheema RAOUS, Manonmani LM. Preliminary study on circulating immune complexes in Bancroftian filariasis. Indian J Med Res. 1982;76:146–50.
46. Kaliaraj P, Harinath BC, Ghirnikar SN. Detection of antigens and antibodies in filarial sera by counter current immune electrophoresis. Curr Sci. 1977;46:603.

47. Lunde MN, Paranjape R, Lawley TJ, Ottesen EA. Filarial antigen in circulating immune complexes from patients with Wuchereria bancrofti filariasis. Am J Trop Med Hyg. 1988;38(2):366–71.
48. Ramaprasad P, Prasad GBKS, Harinath BC. Microfilaraemia, filarial antibody, antigen and immune complex levels in human filariasis before, during and after DEC therapy. Acta Trop. 1988;45:245–55.
49. Ngu JL, Chatelanat F, Leke R, Ndumbe P, Youmbissi J. Nephropathy in Cameroon: evidence for filarial derived immune-complex pathogenesis in some cases. Clin Nephrol. 1985;24(3):128–34.
50. Klei TR, Crowell WA, Thompson PE. Ultrastructural glomerular changes associated with filariasis. Am J Trop Med Hyg. 1974;38(4):608–18.
51. Weil GJ. Antigenemia in lymphatic filariasis. ExpParasitol. 1990;71:353–6.
52. Norões J, Dreyer G, Santos A, Mendes VG, Medeiros Z, Addis D. Assessment of the efficacy of diethylcarbamazine on adult Wuchereria bancrofti in vivo. Trans R Soc Trop Med Hyg. 1997;91(1):78–81.
53. Langhammer J, Birb HW, Zahner H. Kidney disease in lymphatic filariasis: evidence for tubular and glomerular disorders at various stages of the infection. Trop Med Int Health. 1997;2(9):875–84.
54. Remuzzi G, Bertani T. Is glomerulosclerosis a consequence of altered glomerular permeability to macromolecules? Kidney Int. 1990;38(3):384–94.
55. Olson JL, Hostetter TH, Rennke HG, Brenner BM, Venkatachalam MA. Altered glomerular permselectivity and progressive sclerosis following extreme ablation of renal mass. Kidney Int. 1982;22(2):112–26.
56. Schwartz MM, Bidani AK, Lewis EJ. Glomerular epithelial cell function and pathology following extreme ablation of renal mass. Am J Pathol. 1987;126(2):315–24.
57. Pereira AB. Laboratory study of proteinuria. J Bras Nefrol. 1992;14(1):7–11.
58. Waller KV, Ward KM, Mahan JD. Wismatt, DK- Current concepts in proteinuria. Clin Chem. 1989;35(5):755–65.

23 Kidney Involvement in American Cutaneous Leishmaniasis

Rodrigo Alves de Oliveira, Guilherme Alves de Lima Henn, Paulo Sérgio Ramos de Araújo, and Claudio Gleidston Lima da Silva

23.1 Introduction

Leishmaniasis is a group of cosmopolitan diseases with a wide spectrum of presentation, but with a large and important incidence in the tropical zone. As a disease, it has two forms: a visceral form, involving structures of the hemolymphopoietic system, and a second form, with cutaneous and/or mucosal involvement, most often without visceral involvement. The latter is known as cutaneous leishmaniasis (CL). CL occurs in Africa, Asia, Europe, South, Central, and North America, and is endemic in 88 countries, according to WHO, with approximately 12 million infected individuals, with 1.5–2 million new cases every year and 350 million individuals exposed to the infection; the resistance to antimonial drugs [1] is an aggravating factor in some regions of the planet [2]. It is noteworthy that the transmission has not been described in Australia, due to the absence of the parasite in this region of the planet. The absence of the parasite on this continent is explained based on phylogeomorphology. Australia separated well before the African-American bloc, when vectors existed but not the parasites [3].

Ancestors of the current CL-transmitting insects have been described in fossils of the Jurassic period, dated 160,000,000 years ago. Regarding the etiological agent, a monoxenic ancestor, called ***Sauroleishmania***, was identified in cold-blooded ani-mals in the Cretaceous period, 120,000,000 years ago [3]. Evolution has determined the diversification of species and survival in two distinct living environments, one in the insect vector gut, another in the intracellular environment of vertebrate hosts [3]. In the Old World, CL is observed from Senegal, in Africa, to India, Mongolia, Southern France, and Namibia [4], historically known as the Eastern button, Delhi button, and Aleppo button [5].

Balthazar Ramirez, in 1580, seems to have been the first to describe cutaneous leishmaniasis in the Americas, although it had been present in the Old World for centuries [6]. In pre-Columbian America, Inca figures show degenerative lesions of the nostrils, "*huacos,*" consistent with the mucocutaneous form of CL [7]. Only in 1885, the parasite was described by Cunninghan in India, in a case of visceral leish-maniasis. Four years

R. A. de Oliveira (✉)
School of Medicine, Federal University of Pernambuco, Caruaru, Pernambuco, Brazil
e-mail: alves_rodrigo1970@hotmail.con

G. A. de Lima Henn
Department of Community Health, Federal University of Ceara, Fortaleza, Ceara, Brazil

P. S. R. de Araújo
School of Medicine, Federal University of Pernambuco, Recife, Pernambuco, Brazil
e-mail: paulo.raraujo@ufpe.br

C. G. L. da Silva
School of Medicine, Federal University of Cariri, Barbalha, Ceara, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_23

later, Borovsky described the parasite in the cutaneous form of the disease [8].

23.2 Epidemiology

Cutaneous leishmaniasis transmission occurs due to the geoecological and climatic conditions that provide a rich fauna of vectors and potential sources of blood meal, such as small wild vertebrate mammals, especially marsupials and rodents, config-uring cutaneous leishmaniasis primarily as a zoonosis. Thus, in the New World, man would be accidentally infected by entering the wild environment [3].

American cutaneous leishmaniasis (ACL) is considered an occupational disease in forest workers, explaining the high prevalence of CL among Brazilian Army sol-diers training in the Amazon Rainforest, highway construction workers, prospec-tors, hunters, and oil industry and wood workers.

The American cutaneous leishmaniasis no longer behaves as an essentially rural disease in the states of Ceará [9] and Rio de Janeiro [10], which show records of the periurban characteristic of the disease.

Three profiles of cutaneous leishmaniasis are described in Brazil: (1) The essen-tially wild type, with epidemic outbreaks associated with the clearing of forests, as seen in the Brazilian Amazon Forest. (2) The periurban type, described in old colonized areas, associated with domestic canine and domesticated mammalian reservoirs, observed in the Southeast and Northeast regions of Brazil. (3) A third, the modified wild type, described in areas of residual Atlantic forest, appearing as sea- sonal outbreaks, as observed in Caratinga, Viana, Mariluz, Crato, Barbalha, and Baturité [11].

23.2.1 Leishmania

The *Leishmania* is a protozoan that exists in two forms, a flagellate or promastigote, a free-living form present in the digestive tract of vectors, and another, the aflagellate or amastigote form that develops in the cells of the mononuclear phagocytic system of the vertebrate host. The parasite reproduces by binary fission, has a double plasma membrane, a cytoplasm with microtubules, vacuoles, granules, a nucleus, and a kinetoplast (giant mitochondria). The parasite is well visualized with Romanowsky staining, showing a blue nucleus and a pinkish kinetoplast [5]. We emphasize the importance of the plasma membrane that has complex molecules, an important element in parasite tropism and virulence. Among these molecules, gp63 and LPG stand out, which favor the internalization of the parasite and facilitate its survival inside the macrophage phagocyte vacuoles [12]. The gp63 molecule has acid protease activity, promoting the clearance of C3 from the complement system [13]. LPG is expressed on the plasma membrane of all virulent *Leishmania* species, interacting with integrins (p150, 95) and CR3 receptors expressed on the macro- phage membrane, allowing their interaction and internalization [14].

From a taxonomic point of view, the WHO in 1996 joined the leishmanias from New World into two subgenera, ***Viannia*** and ***Leishmania***, with several phenotypic complexes. In the first one, the parasite develops in the insect's posterior gut; in the second, it develops in the middle and anterior guts [5].

23.2.2 Vector

This is a winged, dipterous insect of the genus ***Lutzomyia*** in the New World and ***Phlebotomus*** in the Old World [15]. In Brazil, they are small insects, measuring up to 03 mm in length, known as "*birigui,*" "*mosquito-palha,*" "*cangalhinha,*" "*asa de palha,*" "*arrepiada,*" "*tatuquira,*" and in Cariri they are known as "*borrachudos*"; being frequent in warm months and scarce in cold months, they have positive phototropism and only the female is hematophagous, while the males are frugivores; their life expectancy can reach 27 days; copulation usually occurs at rest. However, it may occur in mid-flight, after which the female lays 40–70 eggs in a humid and dark place, rich in organic

matter. They show better development at temperatures ranging between 25 and 27 °C. The females, which are the vector insects, show twilight and post-twilight activity. The flight distance ranges from 43 meters to 2 kilometers. It is noteworthy that the *Phlebotomus* transmit not only leishmaniasis, but also the 3-day fever and Carrión's disease [5, 16].

23.2.3 Biological Cycle

The biological cycle of any leishmania has two phases. The first occurs during the blood meal; the swallowed amastigote forms undergo transformation in the vector's gut into the promastigote forms. After 3–4 days, free promastigotes reach the pharynx, transforming into the infectious forms [3]. The second phase occurs when the infected female bites the vertebrate host during the blood meal and regurgitates infecting promastigotes. It is estimated that the female is able to inoculate up to 1000 parasites. Subsequently, there is an interaction of the leishmania with neutro phils, eosinophils, and mast cells. In vitro studies have demonstrated the interaction of pg63 and LPG proteins, present in the cell membrane of infecting leishmanias, with integrins present on the surface of antigen-presenting cells, CR3, and p150-95 [13, 17]. Then, nonimmune individuals activate the complement through the classical pathway, opsonizing the parasite with C3b, which will activate the phagocytosis via C3b—CR1 and CR3 receptor, present on the surface of macrophages [14, 18]. The promastigote forms, after the phagocytosis, become amastigotes resistant to enzymatic action, now residing inside the macrophages. The binary fission occurs until they rupture, releasing new parasites in the interstitium [11, 19]. If the phlebotomus has access to this site, the cycle may restart.

23.3 Pathogenesis

After the Phlebotomus' meal, amid the blood, saliva, and promastigote forms are deposited at variable numbers up to 1000 [17, 20]. Different forms of infection can be observed depending on the inoculum and the quality of the insect salivary mate-rial [21, 22].

The escape mechanisms start as soon as the parasites reach the host, and phos-phorylated kinases are released, degrading the complement at the injury site, inhib-iting the classical and alternative pathway, serving as the perfect escape mechanism [13]; simultaneously, the parasite determines the inhibition of IL-12 production by LPG, present in the leishmania membrane [23]. The inflammatory process develops at the site of the blood meal, with the incursion of neutrophils, eosinophils, and macrophages, which can phagocyte the parasite [24]. Dendritic cells and intact macrophages will carry parasites that will proliferate as the amastigote form. Some of these parasitized phagocytic cells will migrate to the regional lymph node. Simultaneously, at this initial time, mast cells, activated leukocytes, and even keratinocytes will produce chemokines and cytokines, which will assist in the interaction of antigen-presenting cells with lymphocytes. As a result, two response patterns can be observed.

23.3.1 Th1 Response Pattern

The initial moments of the infection will determine the pattern of lymphocyte response. Interferon-gamma production by NK [25] cells, on the days following the blood meal, determines the production of Interleukin-12 by antigen-presenting cells, exhibiting an amplifying effect on interferon-gamma production by NK [26] cells. The production of this cytokine is important for the differentiation of naive lymphocytes into Th1 pattern lymphocytes, and the simultaneous suspension of Th2 [27] lymphocyte differentiation. It is worth noting that the type of sensitized anti-gen-presenting cell will be important in defining the type of response determined by the sentinel lymph node. Nodal sensitization by Langerhans cells will determine a Th1-pattern response associated with the cure of the infection [28]. This type of response exhibits elevated IFN γ expressions and the emergence of TNF-α,

trigger-ing macrophage microbicidal mechanisms through the production of NO and free radicals [29, 30], resulting in infection control and cure.

23.3.2 Th2 Response Pattern

This type of response is characterized by high levels of IL-4, IL-10, IL-13, and TGF-β production [31]. The aforementioned cytokines exhibit the opposite effect of Th1 pat- tern response cytokines. IL-4 is produced by leukocytes and CD4+ T lymphocytes [32, 33]; one of its functions is chemotaxis for macrophages, which, in turn, are not activated, and will serve as a reservoir for leishmanias. Moreover, IL-4 prevents the migration of Langerhans cells to the lymph nodes [34]. This passage event is potenti-ated by IL-10. Therefore, it can be observed that, in the occurrence of the aforemen-tioned events, at the site of the blood meal, macrophages infected by amastigotes or promastigotes will go to the sentinel lymph node as the main antigen-presenting cell, with nonfunctional presentation of class I and II MHC molecules, resulting in the Th2 response pattern. That is, sensitized lymphocytes will not be able to synthesize IL-12 [35]. Simultaneously, this macrophage will start producing reasonable amounts of IL-10 [36]. This will result in macrophage deactivation and inhibition of IFN-γ [37] production, resulting in the installation of appropriate conditions for the permanence and development of the leishmania and, consequently, of the disease.

23.4 Diagnosis

The diagnosis of cutaneous leishmaniasis shows a wide spectrum, some with sensi tivity below 50%. Therefore, more than one of the criteria is often used to establish the diagnosis with certainty [38]. The clinical diagnosis of CL is based on morphological aspects, considering clinical and epidemiological aspects [39]. The primary lesion is usually single and may exhibit multiple lesions due to several bites by the vector [40]. The incubation period varies from 10 days to 3 months, starting with an erythematous papule that slowly progresses to a nodule and ulceration. The presence of satellite adenopathy with or without lymphangitis is not uncommon. Although the most frequent presentation is the crateriform ulcer, other forms have been observed, such as impetigo, lichenoid, lupoid, tuberculosis, even vegetating. The literature shows a bubonic form with lymphadenopathy, preceding the appearance of ulceration some weeks before, which may not occur [41].

The definitive diagnosis only occurs with the identification of the parasite through parasitological, immunological, histopathological, and molecular tech-niques. The simplest technique is the direct screening for the parasite on scarified material [42]. Leishmania culture is relatively satisfactory in culture media, with a sensitivity of approximately 50% [43]. Less often, inoculation is used in laboratory animals, preferably hamsters (*Mesocricetus auratus*) [44]. Studies have shown that the histopathological analysis is not effective as the primary method of parasitological diagnosis [45]. Polymerase chain reaction (PCR) is a method with high sensitivity and specificity (sensitivity of 98.41% and specificity of 95.59% [46]) capable of detecting small amounts of leishmania DNA, the equivalent to 1/10 of the parasite [47]. The Montenegro Intradermal Reaction (MIR), recommended by Montenegro in 1926, is still widely used and useful today [48]. The test becomes positive 1 week after the appearance of the skin lesion, but it does not differentiate between the current and the past disease. It is usually negative in diffuse skin forms and in immunocompromised patients [48, 49]. Indirect immunofluorescence reaction (IMF) is a regularly used method, with sensitivity of over 60% in cutaneous forms, 100% in the mucocutaneous form, and negative in diffuse forms; however, it has low specificity and may cross-react with Chagas disease and kala-azar [50]. A positive serology is directly proportional to the parasitism. After the treatment and cure, titers tend to drop and disappear within months [51].

23.5 Clinical Picture

23.5.1 Localized Cutaneous Form

The skin lesion occurs approximately 2 weeks to 2 years after the insect bite and is most common in exposed areas of the skin such as the forearms, legs, neck, and face. Initially, there is a small erythematous papule that, during the evolution, devel- ops into a plaque or nodule, with frequent enlargement of satellite lymph nodes. Spontaneous involution of the nodule or formation of painless ulceration may occur, most often rounded, with raised edges and a hyperemic bottom, which may contain little serous or blood secretion, in addition to the presence of a surrounding ery-thematous halo that gives the lesion a "volcanic" appearance [52–55] (Fig. 23.1).

In 30% of cases, there may be multiple ulcers (up to 20 lesions in the same body seg-ment), distributed in other areas of the skin. Atypical forms have been described, which present as vegetative, verrucous, ulcerated nodules, and lymphangitic lesions. Ulcers may eventually be complicated with secondary bacterial infection with *Staphylococcus* and/or *Streptococcus*[56]. The main differential diagnoses are paracoccidioidomycosis, sporotri-chosis, chromoblastomycosis, cutaneous tuberculosis, skin cancer (such as basal and squamous cell carcinoma), as well as varicose ulcers. Rarely, hematogenous dissemination of parasites may occur with the appearance of multiple skin and nasal mucosa lesions, which seems to be more common in immunosuppressed individuals [53, 54].

Fig. 23.1 Localized cutaneous leishmaniasis. (Source: Manual on Surveillance and Case Management of Leishmaniasis, Ministry of Health, Brazil, 2017)

23.5.2 Disseminated Skin Form

This form occurs in less than 2% of all cases of cutaneous leishmaniasis, and multiple skin lesions, such as papules, nodules, infiltrated plaques, and ulcers, may occur with greater distribution on the face and upper limbs, usually occurring in the first 3 months from disease onset [55]. Individuals living with HIV/AIDS often have more severe conditions, including visceral impairment. The differential diagnosis should be made with histoplasmosis and cryptococ-cosis [53].

23.5.3 Mucosal Form

It is initially characterized by signs and symptoms arising from the inflammatory process in nasal passages. The initial complaint is usually nasal obstruction with the presence of poorly defined discomfort and serous or serosanguineous nasal dis- charge. The physical examination can disclose only nasal septal hyperemia in the early stages, and, with disease evolution, it is possible to detect the presence of an ulcerated or ulcerative-infiltrative lesion, which can lead to destructive lesions of the nasal cavity, with septum destruction and collapse of the nasal pyramid; in the most severe cases, there may be pharynx, larynx, palate, and lips involvement. These cases often cause major damage, such as alterations in the anatomy of the face, which can

cause negative effects on mental health [56] and even cause death from airway obstruction and bronchoaspiration pneumonia. The mucosal form may occur months or years after an episode of cutaneous leishmaniasis, usually in cases where spontaneous healing has occurred; the frequency of occurrence is estimated to be less than 3% of the cases. The main differential diagnoses are paracoccidioidomy-cosis, leprosy, histoplasmosis, syphilis, lymphomas, and squamous cell carcinoma [53–55, 57].

23.5.4 Diffuse Form

A rare and severe clinical form occurs in individuals with specific deficiency in cel-lular immune response to *Leishmania* antigens. It begins with a single lesion that slowly develops into plaques and multiple nonulcerated nodules in large areas of the skin. Its main differential diagnosis is with Virchowian Leprosy [55, 57, 58].

23.6 Kidney Impairment in ACL

Kidney dysfunction related to visceral leishmaniasis is well described in the literature with variable reports, ranging from nonspecific alterations, identified in the urine tests, to several types of glomerulopathies [59–61] (see Chap. 16).

Literature data on kidney impairment in American cutaneous leishmaniasis (ACL) are scarce, and most studies are related to kidney dysfunction associated with pen-tavalent antimonial treatment. These agents are still used as the drug of choice in many centers. They are eliminated by kidney excretion rapidly after the administration. Therefore, caution should be taken in patients who have some degree of kidney dysfunction at the beginning of treatment.

A urinary concentration defect due to the heavy metal present in the drug has already been described by Cucé et al. [62]. Rodrigues et al. [63] described acute kidney injury (AKI) due to massive deposition of immunocomplexes in the glomeruli through the leishmania breakdown by antimonial agents. Sampaio et al. [64] also reported AKI in 11 patients who received a double dose of pentavalent antimonial for 30 days. Among these patients, eight showed a reduction in glomerular filtration rate at the end of the treatment, as well as proximal and distal kidney tubular dysfunction, decreased ability to concentrate urine, and increased sodium excretion fraction. Another mechanism by which the drug can lead to AKI is through a hypersensitivity reaction causing acute tubulointerstitial nephritis [62].

Veiga et al. [65] also demonstrated that leishmania-infected laboratory rats treated with an intraperitoneal antimonial agent developed reduced glomerular fil-tration rate (GFR) and inability to concentrate urine and attributed the latter defect to a drug-induced antidiuretic hormone resistance.

When pentavalent antimonials are used at low doses and for a short period of time, the chances of inducing kidney dysfunction are low. During the treatment of ACL, in many cases it is necessary to use higher doses and for longer periods, increasing their kidney toxicity.

Since these studies are scarce and old, there is a question as to whether ACL alone can induce kidney dysfunction or whether the findings are secondary to its specific treatment; with that in mind, Oliveira et al. studied 37 patients with ACL before starting treatment with meglumine antimoniate [66].

Thirty-seven patients with an ACL diagnosis (epidemiological, clinical, and his-topathological) were studied. All underwent kidney function tests (glomerular and tubular) before starting the specific treatment. The mean age was 35.6 ± 11.7 years, comprising a sample of young patients in which findings of kidney dysfunction could not be attributed to advanced age. Approximately 51.4% of the patients were males.

When comparing the study group with the control group, no significant changes in glomerular function were observed (109.6 ±32 vs. $116 \times 3 \pm 23$ mL/min per 1.73 m^2, $P = 0.694$), and none of the patients had GFR <60 mL/min per 1.73 m^2, which suggests that ACL does not seem to cause direct GFR impairment in this assessed population.

When studying the tubular function of these patients, a decreased ability to con-centrate urine was evident, when compared to the controls. Approximately 77% of them were unable to generate a urine osmolarity (U_{osm})/plasma osmolarity (P_{osm}) ratio >2.8. A urinary acidification defect was also found in 40.5% of patients unable to reduce urinary pH below 5.5. The combined concentration and acidification defects were seen in 12 of 37 patients. Only five patients had no evidence of tubular dysfunction.

The alterations in urinary concentration and acidification found in the study are summarized in Fig. 23.2.

These tubular defects were confirmed in this study through the screening for urinary exosomes, which are corpuscles secreted to the tubular lumen along all nephron segments. These exosomes contain proteins that may be altered in quantity or physical properties in several nephropathies. For example, aquaporin 2 (AQP2) is secreted into the tubular lumen by exosomes and its amount present in urine corre-lates with its expression in kidney tissue [67–69]. After AQP2 was identified, several other urinary transporters were also discovered and started being used in the study of tubular dysfunctions [69]. These membrane transporters are naturally expressed as high-molecular-weight complexes and can be identified in urine [70], which is a noninvasive method to identify biomarkers for the diagnosis of several kidney diseases [71, 72]. The most relevant and most often studied are AQP2, NHE3, NKCC2, H+ -K+ ATPase, and pendrin [73].

Oliveira et al. demonstrated that patients with urinary concentration defect had higher AQP2 expression associated with higher NKCC2 expression, when com-pared to control, which could be a compensatory mechanism, as shown in Fig. 23.3.

The higher urinary expression of the transporters associated to urinary acidifica-tion processes, identified in patients in relation to the controls, helps to corroborate the hypothesis that the inability to acidify the urine in these patients could be caused by ACL. Figures 23.4 and 23.5 show the expression of these transporters in relation to the control.

Based on these data, the author [8] suggests that defects in tubular function, even without clinical expression and without GFR alteration, may be induced by ACL. However, further studies should be performed with a larger sample size and greater use of urinary transporters.

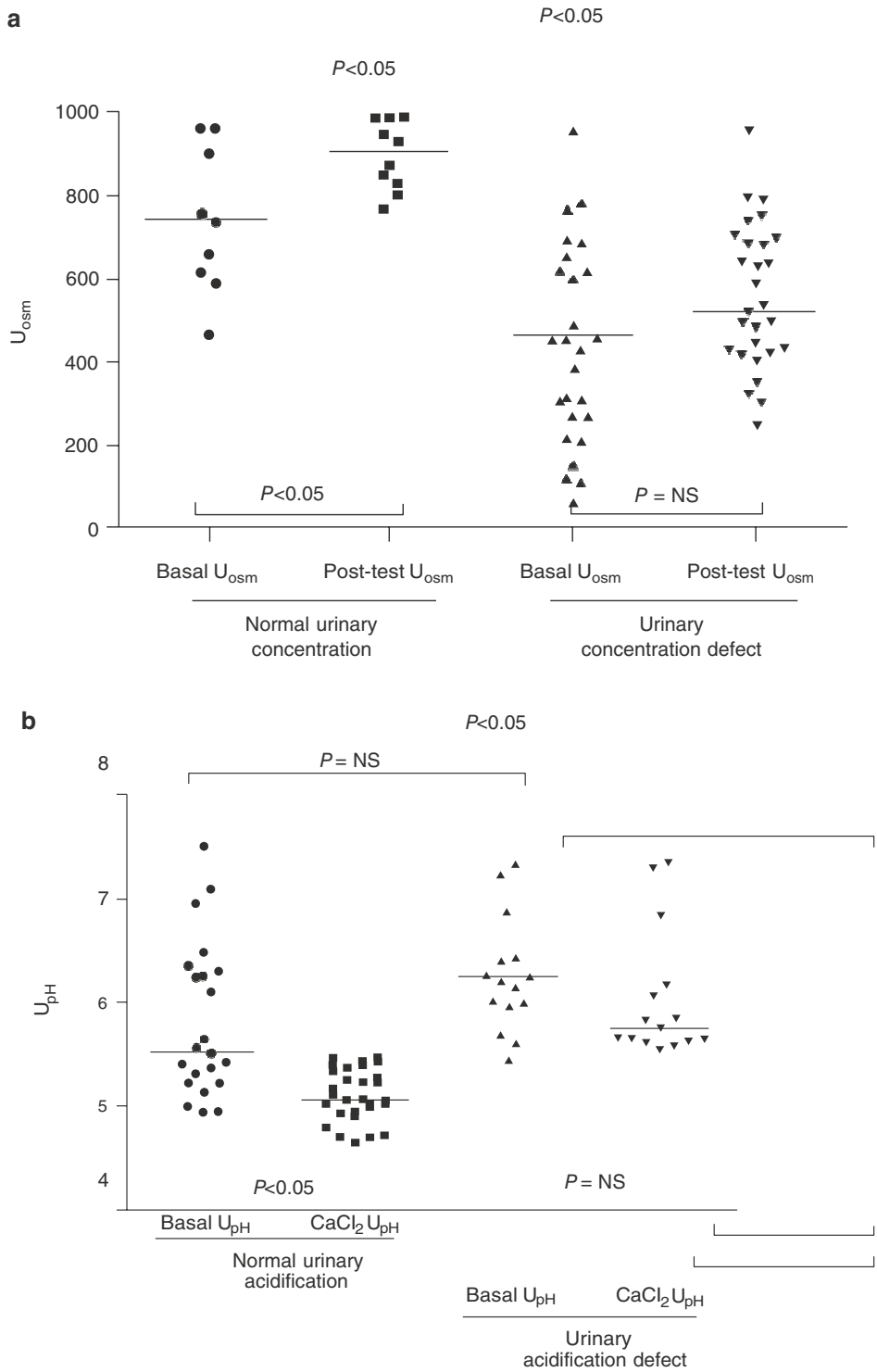


Fig. 23.2 Urinary concentration and acidification capacity in patients with pre- and post- desmopressin and before and after an acidification test with $CaCl_2$. (**a**) Pre- and post-desmopressin Uosm in patients with ACL, with normal and altered urinary concentration capacity. (**b**) Pre- and post-CaCl2 UpH in patients with ACL, with normal and altered urinary acidification capacity. ACL American cutaneous leishmaniasis, NS nonsignificant, Uosm urinary osmolarity, UpH urinary pH. (Adapted from Oliveira et al. [67] with permission. © 2011 International Society of Nephrology)

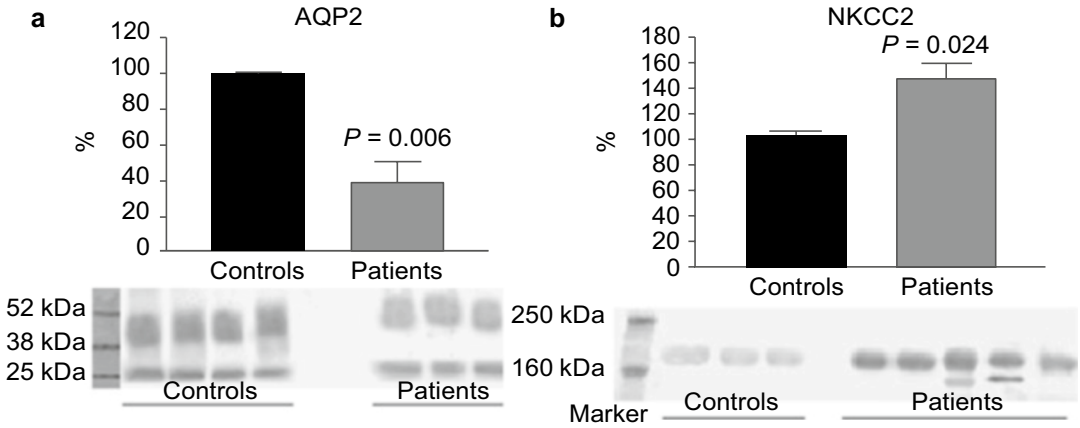


Fig. 23.3 Western blot analysis of urinary exosomes of patients with ACL and the control group. (**a**) aquaporin (AQP2). (**b**) Na-K-2Cl (NKCC2) co-transporter. (Adapted from Oliveira et al. [66], with permission. © 2011 International Society of Nephrology)

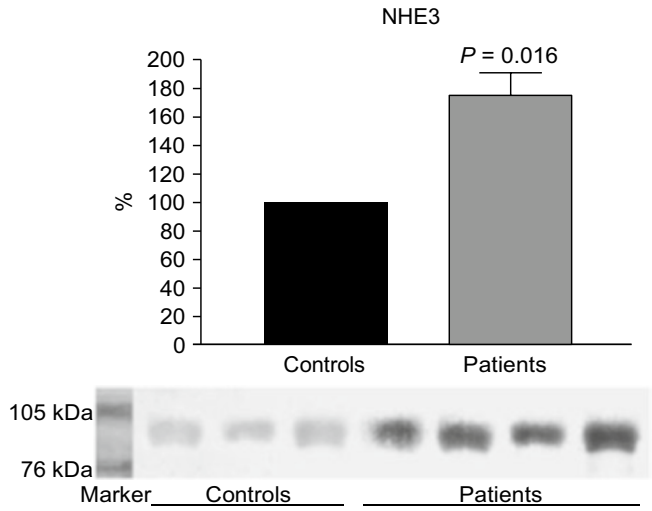


Fig. 23.4 Abundance of NHE3 by Western Blot in urinary exosomes in patients with ACL. (Adapted from Oliveira et al. [66], with permission. © 2011 International Society of Nephrology)

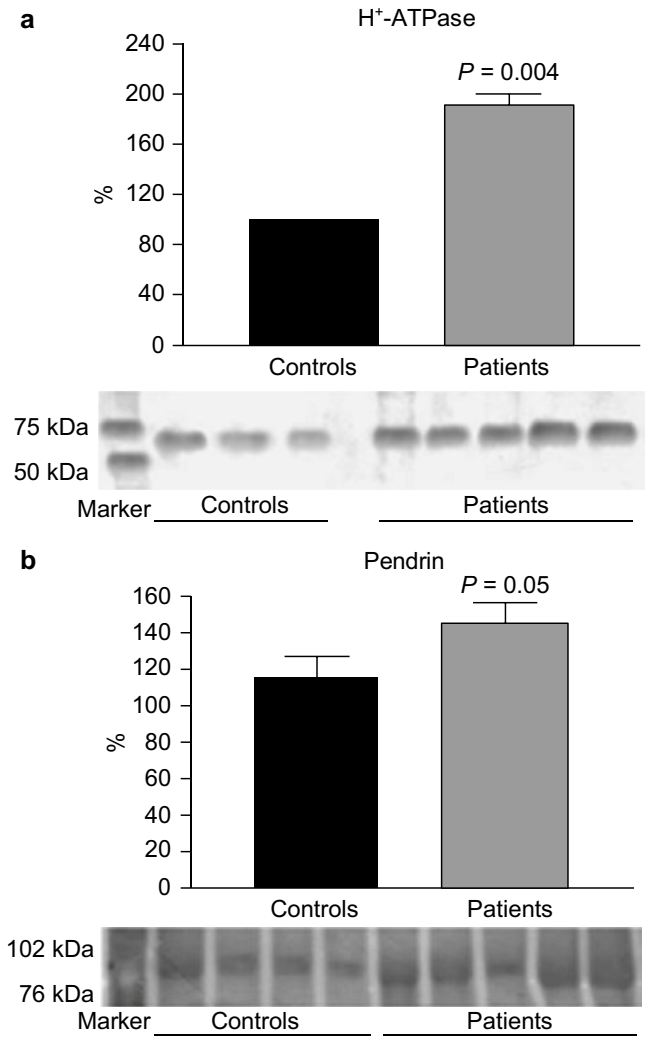


Fig. 23.5 Western blot analysis of urinary exosomes of patients with ACL and control group. (**a**) H + -ATPase. (**b**) pendrin. (Adapted from Oliveira et al. [66], with permission. © 2011 International Society of Nephrology)

23.7 Treatment

Several factors must be considered in the CL care line, so that treatment should be individualized. It then depends on the species involved in the infection, the geographic area of the case, the risk of disseminated disease due to compromised immunological status, and availability of drugs, as well as the number, size, and location of the cutaneous lesions and/or affected mucosal sites. The treatment objectives are as follows: reducing the risk of mucosal form development and disease dissemination, accelerating disease resolution, reducing the risk of lesion recur-rence, attenuating the destructive effects of the lesions, especially on the face, and reducing the transmission of infection [55, 74, 75].

23.8 Parenteral Systemic Therapy

23.8.1 Pentavalent Antimonial

In Brazil, the recommendation is to use meglumine antimoniate at a dose of 10–20 mg/kg/day IV/IM in a single daily dose for 20 days for cutaneous forms and 28 days for mucosal forms. There are no differences between the

administration routes regarding efficacy and safety. Adjustments to the daily dose and/or duration of treatment may be required. The most common adverse effects are arthralgia, myalgia, nausea, abdominal pain, pruritus and, more rarely, kidney injury, pancreatitis, and arrhythmias. It is contraindicated in individuals older than 50 years, those with chronic heart, kidney, and liver disease, and pregnant women [55].

23.8.2 Amphotericin B

- *Amphotericin B deoxycholate* at a dose of 0.7–1.0 mg/kg/day IV (maximum dose of 50 mg/day). The most common adverse effects are fever, chills, cyanosis, palpitations, and dyspnea, in addition to hypomagnesemia and hypokalemia. It may also cause kidney dysfunction and spinal toxicity [55, 74].
- *Liposomal amphotericin B* is better tolerated than the conventional formulation, although few studies have employed this formulation in cutaneous leishmaniasis; the doses are not well established, although some protocols recommend a dose of 2–5 mg/kg/day IV until reaching a cumulative dose of 20–40 mg/kg [55, 74].
- *Pentamidine* 3–4 mg/kg/day IV/IM on alternate days, 3–10 doses depending on the clinical form. It is the first-line treatment for cases of diffuse cutaneous leishmaniasis. Its main severe adverse effects are hypoglycemia, arterial hypotension, arrhythmias, and kidney dysfunction, and may later cause diabetes mellitus [55].

23.9 Oral Systemic Therapy

23.9.1 Pentoxifylline

A peripheral vasodilator with hemorheological properties has been used as an adjunct therapy in the treatment of cutaneous leishmaniasis due to its immunomod-ulatory properties. It is always employed in combination with meglumine antimoni-ate and seems to improve cure rates. The oral dose was 400 mg 2–3 times daily. The main adverse effects are facial flushing and hypotension [55].

23.9.2 Miltefosine

This oral drug was approved by the Food and Drug Administration (FDA) in 2014 for the treatment of cutaneous leishmaniasis in children over 12 years old and non-pregnant and nonlactating women. Indications are restricted to use in infections by *Leishmania* (V) *braziliensis*, *Leishmania* (V) *panamensis*, and *Leishmania* (V) *guyanensis*. It has not been approved by the Brazilian regulatory agencies [74].

23.10 Local Therapy

It is employed in cases that show low risk for mucosal dissemination and/or involve-ment. The most common techniques are intralesional injection of meglumine anti-moniate, liquid nitrogen cryotherapy, radiofrequency thermotherapy, and intralesional pentavalent antimonial administration [55, 75].

References

1. Grimaldi G Jr, Tesh R. Leishmaniasis of the New World: current concepts and implications for future research. Clin Microbiol Rev. 1993;6(3):230–50.
2. Grimaldi G Jr, Tesh RB, McMahon-Prat D. A review of the geographic distribution of leishmaniasis in the New World. Am J Trop Med Hyg. 1989;41(6):687–725.
3. Lainsoni R, Shaw JJ. Ecology and epidemiology: New World. In: Peters W, Killik-Kendrick R, editors. The leishmaniasis in biology and medicine. Orlando: Academic; 1987. p. 291–363.
4. Alrajhi AA. Cutaneous leishmaniasis of the old world. Skin Therapy Lett. 2003;8(2):1–4.
5. Pessoa SB, Martins AV. Parasitologia Médica. 10ª ed. Rio de Janeiro: Guanabara-Koogan; 1978. p. p83.
6. Beck S. Spanish colonies and the West Indies 1580–1744. Beck Index. Available at http://san.beck.org/11-4-LatinAmerica1580-1744.html. Accessed at 09h30min do dia 06 de março de 2018.

7. Altamirano-Enciso AJ, Marzochi MCA, Moreira JS, Schubach AO, Marzochi KBF. Sobre a origem e dispersão das leishmanioses cutânea e mucosa com base em fontes históricas pré e pós-colombianas. Hist Cienc Saúde-Manguinhos. 2003;10(3):853–82.
8. Neves DP, Melo AL, Genaro O, Linardi PM. Parasitologia Humana. São Paulo: Atheneu; 1997. p. 34–382.
9. Oliveira Lima JW. Domestic transmission of cutaneous leishmaniasis in Brazil. 1995. 125 f. Tese (doutorado em Saúde Pública). Boston: Harvard School of Public Health; 1995.
10. Kawa H, Sabroza PC. Espacialização da Leishmaniose Tegumentar na cidade do Rio de Janeiro. Cad Saúde Pública. 2002;18(3):853–65.
11. Vasconcelos IAB. Epidemiologie de La Leishmaniose Cutanne dans um Foyer de L'etat du Cera (Bresil). Definition dês Parasites impliques. 1996. 280 f. Tese (doutorado em parasitologia). Paris: L'Universite Paris XII; 1996.
12. Murray HW, Rubin BY, Rothermel CD. Killing of intracellular leishmania donovani by lymphokine-stimulated human mononuclear phagocytes evidence that interferon-gamma is activating lymphokine. J Clin Invest. 1983;72:1506–10.
13. Bogdan C, Rollinghoff M. The immune response to leishmania: mechanisms of parasite control and evasion. Int J Parasitol. 1998;28:121–34.
14. Filho GB. Bogliolo Patologia. 7° ed. Rio de Janeiro: Guanabara-Koogan; 2006. p. 1359–72.
15. Poinar G. *Lutzomyia adiketis sp*. n. (Diptera: Phlebotomidae), a vector of Paleoleishmania neotropicum sp. n. (Kinetoplastida: Trypanosomatidae) in Dominican amber. Parasit Vectors. 2008;1:22.
16. Sharma U, Singh S. Insect vectors of Leishmania: distribution, physiology and their control. J Vector Borne Dis. 2008;45:255–72.
17. Ribeiro JM. Blood-feeding arthropods: live syringes or invertebrate pharmacologists? Infect Agents Dis. 1995;4(3):143–52.
18. Bray RS, Alexander J. Leishmania and the macrophage. In: Peters W, Killick-Kendrick R, editors. The leishmaniasis in biology and medicine. Orlando: Academic; 1987. p. 211–33.
19. Wheeler RJ, Gluenz E, Gull K. The cell cycle of Leishmania: morphogenetic events and their implications for parasite biology. Mol Microbiol. 2011;79(3):647–62.
20. Warburg A, Schlein Y. The effect of post-blood meal nutrition of phlebotomus papatasi on the transmission of Leishmania major. Am J Trop Med Hyg. 1986;35(5):926–30.
21. Gillespie RD, Mbow ML, Titus RG. The Immunomodulatory factors of blood feeding arthropod saliva. Parasite Immunol. 2000;22(7):319–31.
22. Balkaid Y, Kamhawi S, Modi G, Valenzuela J, Noben-Trauth N, Rowton E, Ribeiro J, Sacks DL. Development of a natural model of cutaneous leishmaniasis: powerful effects of vector saliva pre-exposure on the long-term outcome of *Leishmania major* infection in the mouse ear dermis. J Exp Med. 1998;188(10):1941–3.
23. Piedrafita D, Proudfoot L, Nikolaev AV, Xu D, Sands W, Feng GJ, Thomas E, Brewer J, Fereguson MA, Alexander J, Liew FY. Regulation of macrophage IL-12 synthesis by Leishmania phosphoglycans. Eur J Immunol. 1999;29(1):235–44.
24. Pompeu ML, Freitas LAR, Santos MLV, Khouri M, Barral-Netto M. Granulocytes in the inflammatory process of BAL/c mice infected by Leishmania amazonensis. A quantitative approach. Acta Trop. 1991;48:185–93.
25. Scharton-Kersten T, Scott P. The role of the innate immune response in Th1 cell development following Leishmania major infection. J Leukoc Biol. 1995;57:515–22.
26. Sutterwala FS, Mosser DM. The taming of IL-12: suppressing the production of proinflammatory cytokines. J Leukoc Biol. 1999;65:543–51.
27. Leiby DA, Schreiber RD, Nacy CA. IFN-gamma produced in vivo during the first two days is critical for resolution of murine *Leishmania major* infections. Microb Pathog. 1993;14(6):495–500.
28. Pompeu ML. Avaliação da Resposta Imunitária Linfocitária Inicial na Leishmaniose Humana. 2001. 112f. Tese (doutorado em Patologia Humana). Salvador: Universidade Federal da Bahia; 2001.
29. Nathan CF, Murray HW, Wieb ME, Rubin BY. Identification of interferon-gamma as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity. J Exp Med. 1983;158(3):670–89.
30. Mauel J, Corradin SB, Rouiller YB. Nitrogen and oxygen metabolites and the killing of Leishmania by activated murine macrophages. Res Immunol. 1991;142(7):7–80.
31. Scott P, Pearce E, Cheever AW, Coffman RL, Sher A. Role of cytokines and CD4+ T-cell subsets in the regulation of parasite immunity and disease. Immunol Rev. 1989;112:161–82.
32. Brandt E, Woerly G, Younes AB, Loiseau S, Capron M. IL-4 production by human polymorphonuclear neutrophils. J Leukoc Biol. 2000;68(1):125–30.
33. Noben-Trauth N, Hu-Li J, Paul WE. Conventional naïve CD4+ T-cells provide an initial source of IL-4 during Th2 differentiation. J Immunol. 2000;165(7):3620–5.
34. Takayama K, Yokozeki H, Ghoreishi M, Satho T, Katayama I, Umeda T, Nishika K. IL-4 inhibits the migration of human Langerhans cells through the down regulation of TNF receptor II expression. J Invest Dermatol. 1999;113(4):541–6.
35. Marovich MA, MacDowell MA, Thomas EK, Nutman TB. IL-12p70 production by Leishmania major-harboring human dendritic cells is a CD40/CD40 ligand-dependent process. J Immunol. 2000;164(11):5858–65.
36. Ding L, Linsley PS, Huang LY, Germain RN, Shevach EM. IL-10 inhibits macrophage costimulatory activ-

ity by selectively inhibiting the up-regulation of B7 expression. J Immunol. 1993;151(3):1224–34.
37. Kane MM, Morse DM. The role of IL-10 in promoting disease progression in leishmaniasis. J Immunol. 2000;166(2):1141–7.
38. Manson-Bahr PE. Diagnosis. In: The leishmaniasis, vol. 2. London: Peters W & Kilich-Kendrick R; 1987. p. 703–28.
39. Saraiva NGL, Valderrama M, Labrada AF, Holguín C, Navas G, Palma A, Weigle KA. The relationship of *Leishmania braziliensis* subspecies and immune response to disease expression in New World leishmaniasis. J Infect Dis. 1989;159:725–35.
40. Marzochi MC. As Leishmanioses no Brasil: As leishmanioses tegumentares. J Bras Med. 1992;63:82–104.
41. Sousa AQ, Parise ME, Pompeu MM, Coelho-Filho JM, Vasconcelos IA, Lima JW, Oliveira EG, Vasconcelos AW, David JR, Maguire JH. Bubonic leishmaniasis—a common manifestation of Leishmania viannia braziliensis infection in Ceará—Brazil. Am J Trop Med Hyg. 1995;53(4):380–5.
42. Furtado T. Critérios para diagnóstico de LTA. An Bras Dermatol. 1980;65:51–86.
43. Melo MN. Cultivo de Leishmania em meio definido. Estudo de seus requerimentos nutricionais. 1982; 133 f. Tese (doutorado em Parasitologia). Brasil: Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais; 1982.
44. Rojas E, Scorza JV. Leishmania braziliensis: aislamiento de lesiones por inoculación de hámsteres con o sin adición de lisado de glándulas salivares de lutzomyia youngi. Rev Saúde Pública. 1995;29(1):1–5.
45. Ridley DS, Marsden PD, Cuba CC, Barreto ACA. Histological classification of mucocutaneous leishmaniasis in Brazil and its clinical evaluation. Trans R Soc Trop Med Hyg. 1980;74:508–14.
46. Gontijo BA. Reação em Cadeia da Polimerase (PCR) no Diagnóstico da Leishmaniose Tegumentar Americana. Brasil: Tese (Doutorado em Parasitologia) Faculdade de Medicina-Universidade Federal de Minas Gerais; 1997. p. 91p.
47. Brujin MHL, Barker DC. Diagnosis of New World leishmaniasis: specific detection of species of the *L. braziliensis* complex by amplification of kinetoplast DNA. Acta Trop. 1992;52:45–58.
48. José FF, Da Silva IM, Araújo MI, Almeida RP, Bacellar O, Carvalho EM. Avaliação do poder sensibilizante da reação de Montenegro. Rev Soc Bras Med Trop. 2001;34(6):537–42.
49. Gontijo B, Carvalho MLR. Leishmaniose tegumentar americana. Rev Soc Bras Med Trop. 2003;36(1):71–80.
50. Kar K. Serodiagnosis of the leishmaniasis. Crit Rev Microbiol. 1995;21:123–52.
51. Chiaru AC, Mayrink W, Magalhães PA. Reação de imunofluorescência no controle do tratamento da Leishmaniose Tegumentar Americana. Rev Inst Med Trop São Paulo. 1973;15:298–303.
52. Ferreira MS. Leishmanioses. In: Salomão R, editor. Infectologia: Bases Clinicas e Tratamento. 1ª ed. Rio de Janeiro: Guanabara-Koogan; 2017. p. 177–84.
53. Magill AJ. *Leishmania* species: visceral (Kala-Azar), cutaneous, and mucosal leishmaniasis. In: Mandell, Douglas and Bennett's. Principles and practice of infectious diseases. 8a ed. Philadelphia: Editora Elsevier Saunders; 2017. p. 3091–107.
54. Falqueto A, Sessa PA. Leishmaniose tegumentar americana. In: Veronesi-Focaccia. Tratado de Infectologia. 5ª ed. São Paulo: Editora Atheneu; 2015. p. 1841–58.
55. da Saúde M. Secretaria de Vigilância em Saúde. Brasília: Manual de vigilância da leishmaniose tegumentar; 2017.
56. Bennis I, Brouwere V, Belrhiti Z, Sahibi H, Boelaert M. Psychosocial burden of localized cutaneous leishmaniasis: a scoping review. BMC Public Health. 2018;18(1):358.
57. Tirelli F, Roselino AM, Vernal S. Final diagnosis of 86 cases included in differential diagnosis of American tegumentary leishmaniasis in a Brazilian sample: a retrospective cross-sectional study. An Bras Dermatol. 2017;92(5):642–8.
58. Martínez DY, Verdonck K, Kaye PM, Adaui V, Polman K, Lianos-Cuentas A, et al. Tegumentary leishmaniasis and coinfections other than HIV. PLoS Negl Trop Dis. 2018;12(3):e0006125.
59. Salgado Filho N, Ferreira TM, Costa JM. Envolvimento da função renal em pacientes com leishmaniose visceral. Rev Soc Bras Med Trop. 2003;36:217–21.
60. Chaigne V, Knefati Y, Lafarge R, Bronner J, et al. A patient with visceral leishmaniasis and acute renal failure in necrotizing glomerulonephritis. Nephrologie. 2004;25:179–83.
61. Duvic C, Nedelec G, Debord T, et al. Important parasitic nephropathies: update from recent literature. Nephrologie. 1999;20:65–74.
62. Cucé LC, Belda J, Dias W. Nephrotoxicyty to Glucantime® in the treatment of leishmaniasis. Rev Inst Med Trop São Paulo. 1990;32:249–51.
63. Rodrigues ML, Costa RS, Souza CS, et al. Nephrotoxicity attributed to meglumine antimoniate (Glucantime) in the treatment of generalized cutaneous leishmaniasis. Rev Inst Med Trop São Paulo. 1999;41:33–7.
64. Sampaio RN, Paula CD, Sampaio JH, et al. Avaliação da tolerância e nefrotoxicidade do antimonial pentavalente administrado na dose de 40mg Sb^{v}/kg/dia por 30 dias na forma cutâneamucosa de leishmaniose. Rev Soc Bras Med Trop. 1997;30(6):457–67.
65. Veiga JP, Khanan R, Rosa TT, et al. Pentavalent antimonial nephrotoxicity in the rat. Rev Inst Med Trop São Paulo. 1990;32:304–9.
66. Oliveira RA, Diniz LF, Teotônio LO, et al. Renal tubular dysfunction in patients with American cutaneous leishmaniasis. Kidney Int. 2011;80(10):1099–106.

67. Kanno K, Sassaki S, Hirata Y, et al. Urinary excretion aquaporin-2 in patients with diabetes insipidus. N Engl J Med. 1995;332:1540–5.
68. Wen H, Frokiaer J, Kwon TH, et al. Urinary excretion of aquaporin-2 in rats is mediated by a vasopressin-dependent apical pathway. J Am Soc Nephrol. 1999;10:1416–29.
69. Martin PY, Abrahan WT, Leimig X, et al. Selective V2-receptor vasopressin antagonist decreases urinary aquaporin-2 excretion in patients with chronic heart failure. J Am Soc Nephrol. 1999;10:2165–70.
70. Klingemberg M. Membrane protein oligomeric structure and transport function. Nature. 1981;290:449–54.
71. Hewitt SM, Dear J, Star RA. Discovery of protein biomarkers for renal disease. J Am Soc Nephrol. 2004;15:1677–89.
72. Zhou H, Yuen PS, Pisitkun T, et al. Collection, storage, preservation and normalization of human urinary exsosomes for biomarker discovery. Kidney Int. 2006;69:1471–6.
73. Gonzales PA, Pisitkun T, Hofferti JD, et al. Large-scale proteomics and phosphoproteomics of urinary exosomes. J Am Soc Nephrol. 2009;20:363–79.
74. Aronson N, Herwaldt BL, Libman M, Pearson R, Peter Weina L-VR, et al. diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Am J Trop Med Hyg. 2017;96(1):24–45.
75. Centers for Disease Control and Prevention [homepage na internet]. Parasites—leishmaniasis. Resources for Health Professionals. Available at https://www.cdc.gov/parasites/leishmaniasis/health_professionals/index.html. Accessed 20 Mar 2018

24 Nephropathy in Visceral Leishmaniasis (Kala-Azar)

Gdayllon Cavalcante Meneses,
Guilherme Alves de Lima Henn,
Alice Maria Costa Martins,
Michelle Jacintha Cavalcante Oliveira,
and Elizabeth De Francesco Daher

24.1 Introduction

Visceral leishmaniasis (VL), also popularly known as kala-azar, is a severe infectious disease caused by parasites of the genus Leishmania. VL affects thousands of people worldwide each year and is one of the most important neglected tropical diseases, present in almost every continent. In the Americas, VL is caused by the species *Leishmania infantum* (subspecies *chagasi*) [1] and is endemic in Brazil. Disease severity depends on the species of *Leishmania* and the host immune response, being potentially fatal (90%) when untreated [2, 3]. Patients with VL show intense parasitism of the reticuloendothelial system, affecting the liver, spleen, bone marrow, lymph nodes, digestive system, and even the kidneys, with a marked presence of anemia, leukopenia, thrombocytopenia, hypoalbuminemia, and hypergammaglobulinemia [2].

Kidney injury in VL is important and frequent. Acute kidney injury (AKI) affects 46% of hospitalized patients and is associated with increased mortality [4–6]. The causes of AKI in VL are associated with the use of amphotericin B, secondary infections, hemodynamic abnormalities, and systemic inflammation. The main kidney alterations are associated with interstitial nephritis and glomerular alterations.

An early diagnosis of AKI is crucial to prevent other kidney complications, requiring renal replacement therapy and even resulting in death. The delayed diagnosis of kidney disease is partly due to the use of criteria based on a late marker, serum creatinine, such as the RIFLE, AKIN, and KDIGO classification [7]. Therefore, new kidney injury biomarkers are being widely studied in different clinical contexts for the early detection of kidney lesions. Considering that amphotericin B is the most effective treatment against *Leishmania* and is potentially nephrotoxic, early diagnosis of kidney injury is essential for the best clinical management of these patients.

G. C. Meneses
Department of Internal Medicine, Post-Graduation Program in Medical Sciences, Federal University of Ceara, Fortaleza, Ceara, Brazil

G. A. de Lima Henn
Department of Community Health, Federal University of Ceara, Fortaleza, Ceara, Brazil

A. M. C. Martins
Department of Clinical and Toxicological Analyses, Post-Graduation Program in Pharmaceutical Sciences, Federal University of Ceara, Fortaleza, Ceara, Brazil

M. J. C. Oliveira (✉)
School of Medicine, Federal University of Alagoas, Maceio, Alagoas, Brazil

E. De Francesco Daher
Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_24

24.2 Epidemiology

Worldwide, approximately 200–400,000 new cases of leishmaniasis are detected every year, and in 2014, 90% of new cases were concentrated in six countries: India, Ethiopia, Somalia, Sudan, South Sudan, and Brazil, as shown in Fig. 24.1 [1, 8, 9]. Brazil is responsible for 96% of VL cases in the Americas [10]; in 1990, there were 1944 confirmed cases of VL in the country, and in 2015 they increased to 3298. In 2015, there were 272 deaths from VL, with a case fatality rate of almost 8% [11]. During all these years, the Northeast region showed the highest number of occurrences, with 1806 cases confirmed in 2015 alone, representing 55% of all notifications in the country, while the second place, the Southeast region, had less than half of the number of cases [11]. Maranhão, Bahia, Piauí, and Ceará are the states with the highest number of cases and also the highest number of deaths caused by VL. In the state of Ceará alone, the number of confirmed cases is higher than that of other combined South American countries, such as Argentina, Bolivia, Colombia, Honduras, Paraguay, and Venezuela. Moreover, from 2007 to 2015, there was a 42% increase in the number of deaths, with an annual average of 34 deaths and an aver-age case fatality rate of 6.1% [12].

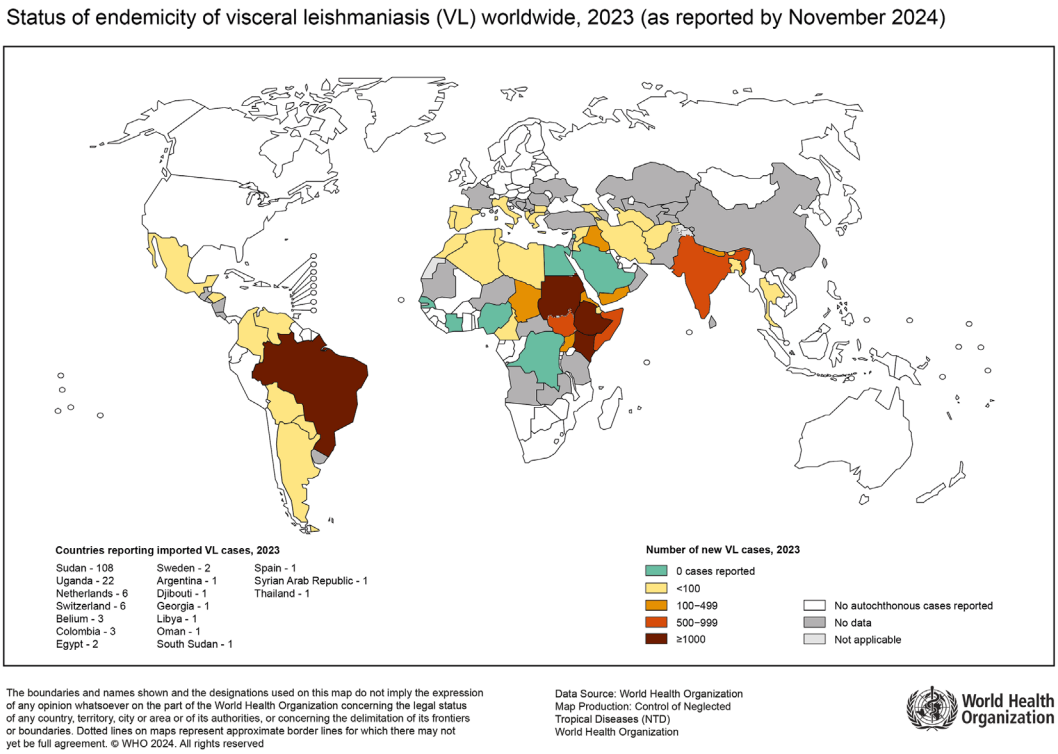


Fig. 24.1 Worldwide endemicity of visceral leishmaniasis in 2023. (Adapted from the World Health Organization [1]. With permission. © 2023 World Health Organization)

24.3 Life Cycle

The genus *Leishmania* consists of protozoa that belong to the family Trypanosomatidae, order Kinetoplastida [12]. The Leishmania has two main mor-phological forms during its life cycle. The metacyclic and flagellated promastigote form is the infectious form of the parasite that lives in the extracellular environment, which is found in the gut of the invertebrate vector; the promastigote form is trans-mitted by the vector saliva when it bites a mammal; and the amastigote form is present in the intracellular environment, inside phagocytic cell vacuoles, mainly macrophages, of mammals [13, 14].

The Leishmania life cycle occurs between mammalian hosts and female vector insects (genera: *Phlebotomus* and *Lutzomyia*) found in tropical and subtropical regions [15]. In Brazil, it is popularly known as the "straw-mosquito" (*mosquito palha*). The cycle begins when female vectors ingest mammalian blood, particularly of dogs and humans, containing macrophages infected with the amastigote form (which is 3–5 μm in diameter). The change in the environmental conditions from the mammalian host to the vector gut, such as a decrease in temperature and a rise in pH, causes morphological transformations in the parasites, which become procyclic promastigotes [15]. Procyclic promastigotes are forms that have a small and fragile flagellum that limits their locomotion. However, after 48–72 h, the parasites start to differentiate andproliferate in the favorable environment, changing into different promastigote forms that reach the insect's intestinal lumen, increasing their movement capacity, until they reach the final and infectious form, the metacyclic promastigote [16].

Inoculation of the metacyclic promastigote forms by the vector into the skin of the susceptible mammalian host causes the infection. In humans, the incubation period is 10 weeks to 24 months, with an average of 2–6 months [12]. The host macrophages phagocytose the promastigotes, which develop into amastigotes and multiply into phagolysosomes [2]. Subsequently, the parasites can spread and infect other cells of the reticuloendothelial system in several tissues, especially in the bone marrow, spleen, liver, and lymph nodes, which can cause several clinical manifestations and complications [17].

24.4 Clinical Manifestations

The incubation period may vary from a few weeks to many years [2]. The infection can be asymptomatic or manifest as a progressive disease, and symptoms may vary according to the endemic area [18]. The patient may have insidious fever, skin-mucous pallor, splenomegaly, associated or not to hepatomegaly, fatigue, weakness, hyporexia, and weight loss. As the disease progresses, the splenomegaly may increase, causing abdominal distension and pain, which may worsen with concomi-tant hepatomegaly [19]. Jaundice and hemorrhage may also occur.

Regarding laboratory alterations, hematological dysfunctions are common in patients with VL. Pancytopenia may occur due to bone marrow suppression and increased splenic sequestration [20]. Fatigue and weakness may be a consequence of anemia, which is caused by the persistent inflammatory status, peripheral destruction of erythrocytes in the enlarged spleen, and also by hemorrhages [19, 21, 22]. Another cause of anemia may be due to alterations in erythropoiesis at the bone marrow level with erythroblast apoptosis induction through cytokine-mediated fac tors [23].

Hyperglobulinemia and hypoalbuminemia are common and important laboratory findings in VL, constituting risk factors for severity and death in multivariate analyses [24]. Hypoalbuminemia occurs due to intense hepatic and intestinal parasitism, leading to decreased albumin production in the liver and less albumin absorption in the intestine, especially in malnourished patients [25]. Liver parasitism causes mononuclear cell infiltration, inflammation, hepatocyte degeneration, and fibrosis [26, 27]. This hepatic impairment may be accompanied by hepatomegaly and ele-vated liver enzymes such as AST (Aspartate Aminotransferase) and bilirubins. Hyperbilirubinemia is a variable strongly associated with VL severity [28].

Hyperglobulinemia occurs due to polyclonal activation of B-lymphocytes in response to Leishmania infection, with elevation of the plasma levels of immuno-globulin [29].

If the diagnosis is not made and treatment is not started, the disease increasingly progresses, with continuous fever and more severe patient involvement, lower limb edema, hemorrhages, jaundice, and kidney injury, which may progress to death [4, 30–33].

24.5 Diagnosis

Early diagnosis and treatment are essential for a good prognosis in patients with VL, and extremely important for disease control, as it interrupts the parasite's life cycle, transmission, and improves symptoms [19].

Diagnostic tests for VL should have high sensitivity and specificity, as the disease is a severe condition and the drugs used in its treatment are potentially toxic [17, 19, 34]. The clinical presentation of VL may be unspecific. However, the reduction in the number of leukocytes and platelets in the blood and polyclonal hypergammaglobulinemia have good specificity but low sensitivity, requiring confirmatory tests [35]. The finding of amastigote forms by microscopy of lymph node, bone marrow, and spleen aspirates is the classic confirmatory test and the gold standard for VL [36, 37]. However, the microscopic examination is more invasive and requires qualified professionals, at the time of both collection and preparation of slides for better accuracy or reliability [38].

Serological tests have been important tools in the diagnosis of VL. Two serologi-cal tests were developed and validated: the direct agglutination test and the immu-nochromatography test, based on the screening of antibodies against recombinant K39 antigen [19]. In practice, the most commonly used diagnostic tools are the parasitological test in bone marrow aspirate and serological examination by rK-39 rapid antigen test, together with clinical and epidemiological data.

Molecular tests (PCR) have represented important scientific advances in the diagnosis of VL. Despite having good sensitivity and specificity (95% and 92%, respectively, in bone marrow), the lack of standardization for the specific DNA and/ or RNA genes to be used is the main factor preventing the wide use of this technique [39, 40].

24.6 Treatment

After the diagnosis has been confirmed, treatment should be started immediately. VL is a severe disease that, if left untreated, is almost always fatal [32]. Care of VL patients ranges from treatment with specific leishmanicidal drugs to the manage-ment of secondary infections, anemia, hypovolemia, and malnutrition [19]. In Brazil, treatment for VL is free of charge and available in the Unified Health System (SUS) service network, being based on the use of three drugs, depending on the medical indication: N-methylglucamine antimoniate, amphotericin B deoxycholate, and liposomal amphotericin B [31].

Antimonials are toxic drugs with frequent adverse side effects that can be life threatening, including cardiac arrhythmia and acute pancreatitis, especially in patients younger than 2 years, in the elderly, and in individuals with signs of advanced disease or severe malnutrition [21]. Amphotericin B deoxycholate has replaced antimonial drugs as the first-line treatment for VL because it is more potent and acts against amastigote and also promastigote forms [19]. However, it also has several side effects, including vascular endothelial toxicity, hypokalemia, pulmo-nary alterations, headache, fever, chills, asthenia, muscle and joint pain, vomiting, and hypotension [41].

Kidney complications are the most important ones and occur in almost all patients during treatment with amphotericin B deoxycholate [42]. The kidney injury mechanisms seem to occur by drug-induced vasoconstriction, decreasing kidney perfusion and glomerular filtration rate, and due to the direct interaction of amphotericin B with the kidney tubular epithelial cell membrane, causing tubular dysfunction, especially at the proximal tubule level [43].

Aiming to reduce nephrotoxicity, other amphotericin B pharmaceutical formulations, the so-called lipid formulations, have been developed [44, 45]. Liposomal amphotericin B (the main representative of these formulations) consists of liposomes with a diameter of 60–70 nm containing amphotericin B inside them. Liposomes have greater affinity for the reticuloendothelial system and are less concentrated in kidney tissue, showing a better therapeutic index and lower nephrotoxicity [44, 46]. Despite the decrease in nephrotoxicity rates with lipid formulations, amphotericin B-associated acute kidney injury is still frequent and may reach 20% in these formulations [42, 47]. Moreover, liposomal amphotericin B treatment represents a high cost to the public service, restricting its use.

24.7 Kidney Injury

Immunological components such as immune complex deposition, T-cell activation, inflammatory processes, and the presence of *Leishmania* in kidney tissue are mainly responsible for kidney injury in patients with VL, especially glomerulonephritis and interstitial nephritis [4, 48–50].

Kidney involvement in VL is frequent and has been reported in several studies. When analyzing clinical findings associated with kidney alterations, we observe moderate proteinuria, hematuria, leukocyturia, microalbuminuria, and hydroelectrolytic disturbances such as hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, increased excretion fraction of various electrolytes, and defects in urinary concen-tration and acidification [6, 23, 47, 48, 50–52].Glomerular injury in VL is characterized as mesangial proliferative lesions or deposition of immune complexes, which can lead to rapidly progressive glomerulo nephritis [4, 48, 53]. Microalbuminuria is a frequent alteration (up to 40%) inpatients with VL, suggesting an important glomerular filtration barrier defect [54, 55]. Moreover, the high proteinuria observed in these patients may be the result of hypergammaglobulinemia, with low molecular weight protein fractions such as alpha1, alpha2, beta-microglobulins, and especially gamma-globulins, which are freely filtered in the glomeruli. Additionally, it can accelerate the progression of kidney disease through chemokine induction and activation of the complement system, which lead to infiltration of inflammatory cells into the kidney interstitium [56].In a literature review of our group, important kidney histological alterations in patients with VL were highlighted. Among the glomerular alterations, mesangial proliferative lesions, mesangial hyperplasia, membranoproliferative glomerulonephritis, segmental and focal sclerosis, and amyloid deposits have been reported in the chronic stage of the disease [4]. Other observed alterations are tubulointerstitial nephritis, which is the most frequent one, followed by reports of interstitial fibrosis, tubular atrophy, and the presence of Leishmania in kidney tissue in immunocompro-mised patients [57].

AKI has been observed with significant frequency (>30% of cases) in VL [54]. AKI has been reported in adults and children, being more severe in the first. Risk factors observed for AKI in adults were hypokalemia, leukopenia, and amphotericin B use [58]. Another study found 34% of AKI in patients with VL, and showed that older age, male gender, and jaundice were important risk factors for AKI, with an odds ratio (OR) of 1.05, 2.2, and 2.9, respectively [6]. In a retrospective study of 146 children, 45.9% developed AKI, especially the younger ones, and it was associated with hyponatremia, hypokalemia, hypoalbuminemia, hyperglobulinemia, and mainly with the presence of secondary infections (OR 3.65) [5]. Studies have sug-gested that the development of AKI hinders the clinical management of patients with VL and is associated with increased hospital length of stay, poor prognosis, and mortality [4, 54].

The diagnosis of kidney disease remains a late one, which contributes to the high rates of AKI in patients [59, 60]. The clinical markers used to assess kidney function, such as urinary volume and serum creatinine, are very limited due to extrarenal variables that interfere with their levels, and creatinine only increases when 50% of the kidney function is compromised [59, 61]. The identification of kidney injury also becomes

difficult due to the lack of sensitivity of diagnostic tests, being often diagnosed only when it is fully established, with obvious clinical signs and symptoms.

Consequently, there has been an exponential increase in studies on new AKI biomarkers that could be used earlier and were more specific for kidney injury [62]. These studies aim to obtain important information regarding the location of kidney injury, assessing the intensity and differential diagnosis of the injury, its predictive capacity for AKI in new or hospitalized patients, and the impacts of therapeutic intervention.

Several candidates for new biomarkers are being studied for different clinical contexts, showing better specificity and sensitivity when compared to classic mark-ers of kidney function [7]. They can be quantified in serum and urine samples, showing relevant results in both. Although urine is ideal for these diagnostic and prognostic studies, as it is a noninvasive test performed in easily collected samples, serum is also a very important specimen, particularly in studies of patients under intensive care, in which urine collection is not possible [63, 64].

Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule- 1 (KIM-1) are among the most often studied biomarkers for AKI [7, 65–69]. Other biomarkers are more specific for glomerulopathies, such as chemokine-monocyte chemotactic protein-1 (MCP-1), which is associated with glomerular inflammation and interstitial nephritis [70].

Glomerular involvement is often present in infectious diseases such as VL, and may be decisive for the development of AKI, contributing to poor patient prognosis. In a pilot study performed by our group, urinary MCP-1 levels were elevated in 19 VL patients compared to the control group [71]. Recently, continuing this pilot study, we detected, in 50 new VL patients, increased levels of urinary MCP-1 and also other new assessed biomarkers at hospital admission: serum and urinary NGAL and urinary KIM-1. For the first time, the role of new kidney biomarkers was investigated in clinical kidney alterations in patients with VL. In this study, increased urinary KIM-1 levels were associated with proteinuria, and urinary MCP-1 was associated with microalbuminuria. Systemic NGAL was associated with glomerular filtration rate, creatinine, and urea (Table 24.1).

Although urinary KIM-1 and urinary MCP-1 levels were elevated in patients who developed AKI, only serum NGAL was associated with the development of AKI in VL (Table 24.2). Moreover, the AKI diagnostic capacity was demonstrated at hospital admission in patients with VL, and only urinary NGAL, and especially serum NGAL, were significant [72] (Fig. 24.2).

NGAL is a protein released by activated neutrophils, an important component of the innate

Table 24.1 Pearson's and Spearman's correlations between kidney clinical parameters and new biomarkers in patients with visceral leishmaniasis

	sNGAL		uNGAL		uKIM-1		uMCP-1	
	r	*p*	*r*	*p*	*r*	*p*	*rho*	*p*
Creatinine (mg/dL)	0.487*	*<0.001*	0.118	*0.481*	0.389*	*0.017*	0.153	*0.359*
Urea (mg/dL)	0.583*	*<0.001*	0.251	*0.152*	0.397*	*0.022*	0.166	*0.349*
GFR (mL/min/1,73m^2)	−0.447*	*0.001*	−0.226	*0.172*	−0.195	*0.248*	−0.294	*0.074*
Sodium (mEq/L)	−0.507*	*0.010*	−0.307	*0.135*	−0.490*	*0.015*	−0.128	*0.542*
Proteinuria (mg/g-Cr)	0.239	*0.221*	0.203	*0.301*	0.419*	*0.030*	−0.159	*0.420*
Albuminuria (mg/g-Cr)	0.350*	*0.031*	0.509*	*0.001*	0.442*	*0.006*	0.455*	*0.004*

Pearson's r; Spearman's Rho. *Significant correlations; $p < 0.05$.GFR, Glomerular filtration rate estimated by the CKD-EPI formula

sNGAL and uNGAL serum and urinary neutrophil gelatinase-associated lipocalin, respectively

uKIM-1 urinary kidney injury molecule-1, *uMCP-1* urinary monocyte chemotactic protein-1

Table 24.2 Correlation models adjusted for variables associated with the development of acute kidney injury in patients with visceral leishmaniasis

	AKI		
	OR	(95%CI)	*p*
Univariate			
uKIM-1 (ng/mg-Cr)	1.380	(0.855 a 2.227)	0.187
uMCP-1 (pg/mg-Cr)	1.001	(0.999 a 1.003)	0.0.321
uNGAL (ng/mg-Cr)	1.102	(0.992 a 1.225)	0.071
sNGAL (for every 10 ng/mL)	1.227	(1.074 a 1.403)	0.003
Adjusted for model 1			
sNGAL (for every 10 ng/mL)	1.254	(1.071 a 1.470)	0.005
Adjusted for model 2			
sNGAL (for every 10 ng/mL)	1.285	(1.014 a 1.628)	0.038

CI confidence interval, *OR* odds ratio
Acute kidney injury defined by KDIGO criteria
sNGAL and uNGAL serum and urinary neutrophil gelatinase-associated lipocalin, respectively, *uKIM-1* urinary kidney injury molecule-1, *uMCP-1* urinary monocyte chemotactic protein-1 *Model 1* age, gender, hemoglobin, leukocytes, platelets, interferon-gamma (IFN-γ), and C-reactive protein (CRP), *Model 2* age, gender, globulins, albumin, AST, IFN-γ, and CRP

antimicrobial immunity in the early stages of infection. Elevated blood NGAL levels also attract neutrophils and activate CD4 + T-regulatory cells [73]. In this context, studies with *Leishmania major* and *L. infantum* (visceral leishmania- sis) have reported the association between innate immunity and initial neutrophil activation [3]. At the initial stage, the metacyclic promastigote forms (infectious flagellate form of Leishmania) are phagocytized by neutrophils that seem to help them escape from macrophage destruction. In these cases, the innate immunity does not control the infection and the systemic disease progresses, showing exacerbated neutrophil activation [3]. In adaptive immunity, antigen-presenting cells (APCs) capture dead parasites and present them to the CD8+ and CD4+ cells. Specifically, the CD4+ T are activated and differentiate into T_H1 cells that produce IFN-γ. IFN-γ seems to inhibit neutrophil recruitment and activate infected macrophages, which can thus kill the parasites [73].

On the one hand, the high levels of systemic NGAL in VL observed in our recent study may be associated with an exacerbated and inefficient neutrophil activation, which contributes to the infection progression. However, the intrinsic kidney injury resulting from VL infection and systemic inflammation can contribute to increase NGAL expression in the nephron segments, causing an additional increase in serum and urinary NGAL [72]. Additionally, decreased tubular resorption and any GFR impairment due to kidney injury contribute to increase systemic and urinary NGAL levels [72] (Fig. 24.3).

Systemic NGAL levels seem to play an important role in predicting AKI in VL. In the same study, it was observed that systemic NGAL was associated early with the development of AKI, showing good diagnostic capacity with a cut-off of 154 ng/mL and AUC-ROC = 0.814 (Fig. 24.2). Urinary NGAL showed lower diag-nostic capacity. Another study that evaluated the diagnostic performance of NGAL analyzed only urinary NGAL in 22 patients with leishmaniasis, 5 of them with VL and 17 with cutaneous leishmaniasis, while undergoing treatment with amphotericin B. Urinary NGAL was elevated in the AKI group and showed better diagnostic performance for AKI on the fifth day of treatment [39].The pathophysiology of kidney injury in VL is summarized in Fig. 24.4.

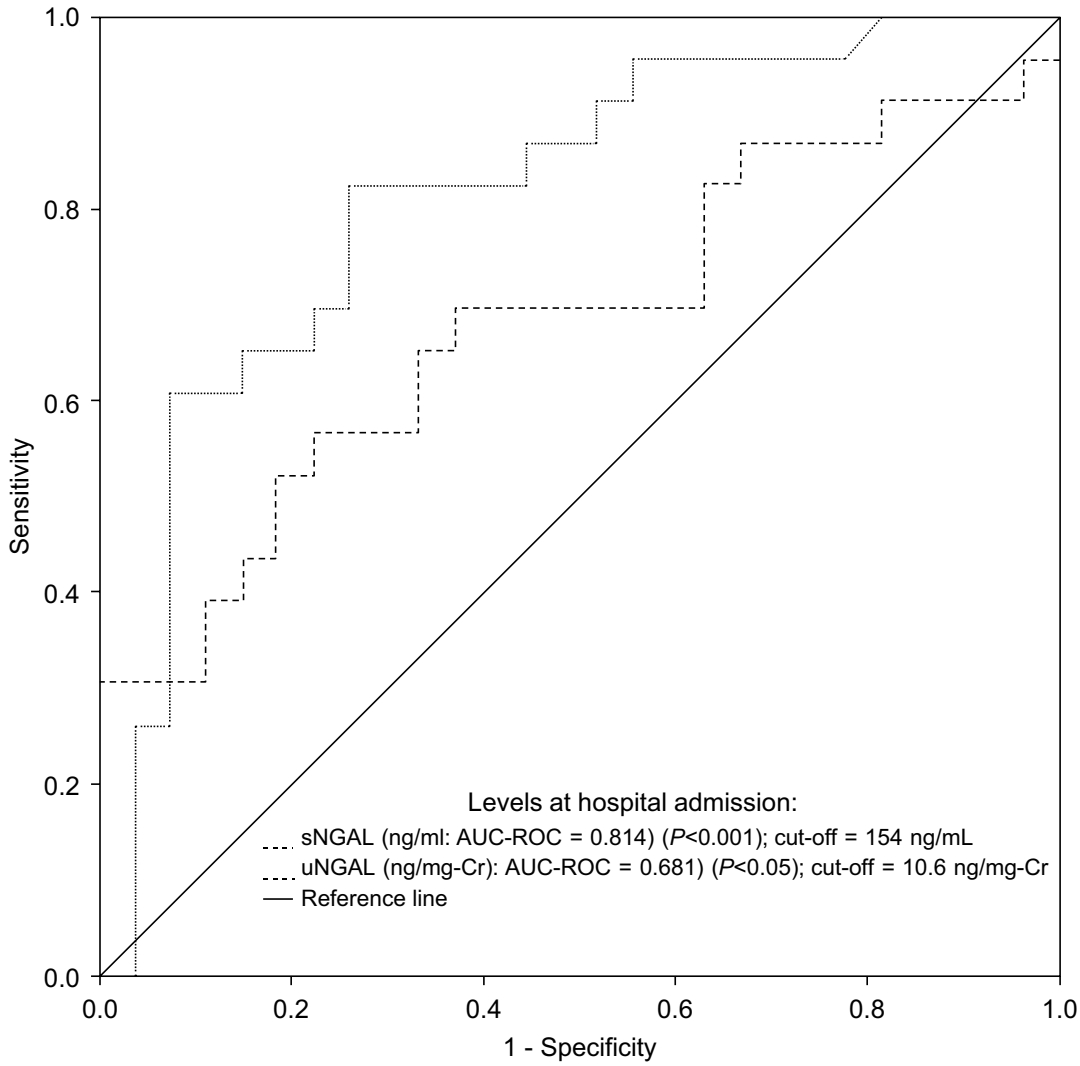


Fig. 24.2 Performance of serum and urinary NGAL levels at hospital admission for diagnosis of acute kidney injury in patients with visceral leishmaniasis. *AUC-ROC* area under the ROC curve. (Adapted from Meneses et al. [72] With permission. ©2018 Federation of European Societies for Tropical Medicine and International Health)

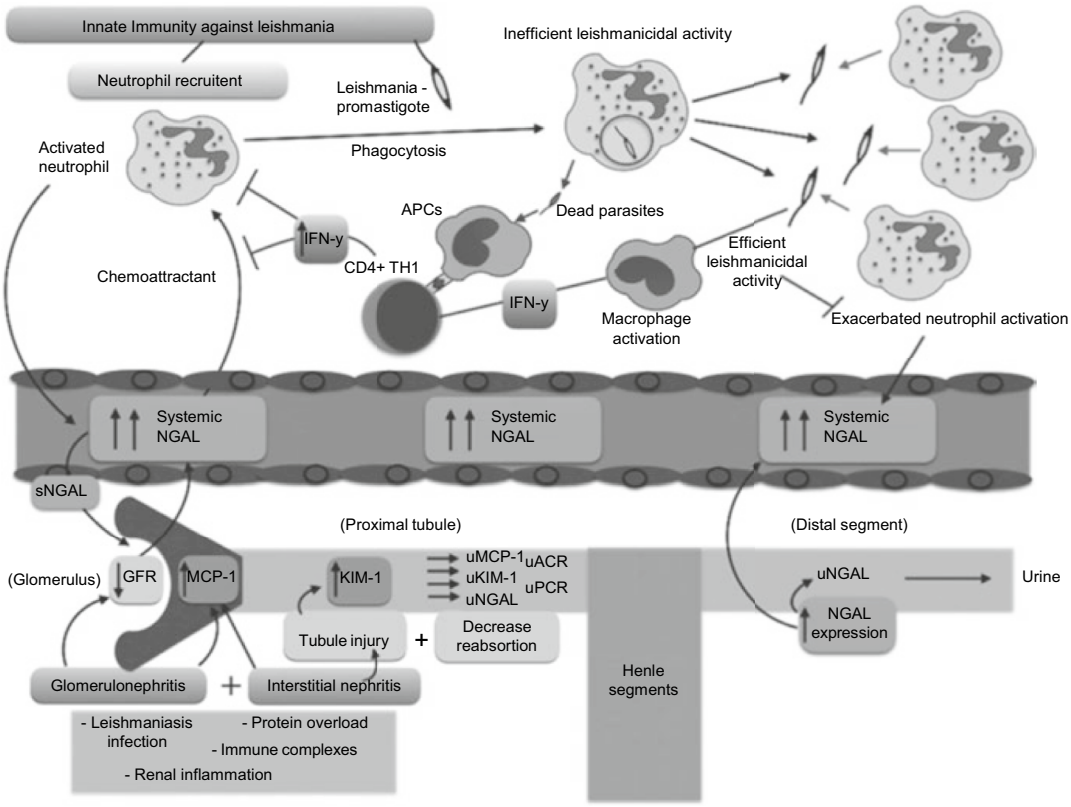


Fig. 24.3 Hypothesis of pathogenic mechanisms involved in the control of leishmania infection and kidney injury in visceral leishmaniasis. (Adapted from Meneses et al. [72] With permission. ©2018 Federation of European Societies for Tropical Medicine and International Health)

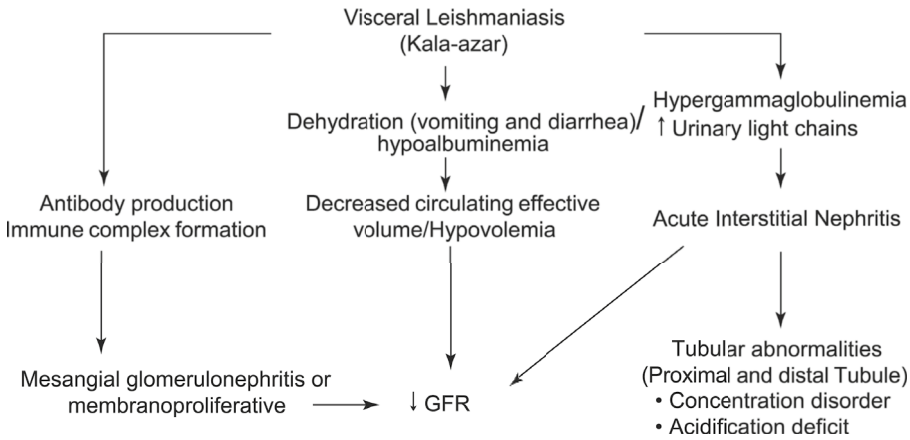


Fig. 24.4 Pathophysiology of kidney injury in visceral leishmaniasis. (Reproduced from Daher e Silva Junior [74]. With permission. © 2018 Editora Guanabara-Koogan, Rio de Janeiro)

24.8 Conclusion

The mechanisms of kidney injury caused by Leishmania infection are not fully understood. Moreover, the clinical diagnosis of kidney injury is not accurate and is a little sensitive, which makes it difficult to identify the type, onset, cause, and severity of kidney injury in patients with VL. Considering that AKI is one of the main complications of VL and is associated with increased mortality [4, 48], the use of new, more specific, and sensitive kidney biomarkers has significant scientific value for the potential diagnosis and elucidation of new kidney injury mechanisms.

Systemic levels of NGAL in patients with VL seem to play an important role in predicting the risk of developing AKI. Moreover, a significant proximal tubular lesion detected by urinary KIM-1 seems to be associated with protein overload in the proximal tubule and dysfunction of the glomerular filtration barrier associated with glomerular inflammation.

References

1. World Health Organization. Leishmaniasis: epidemiological situation; 2023. Available at https://www.who.int/images/default-source/maps/leishmaniasis_vl_2023.png?sfvrsn=94205cef_4. Accessed on 20th Apr 2025.
2. van Griensven J, Diro E. Visceral leishmaniasis. Infect Dis Clin N Am. 2012;26:309–22.
3. Kaye P, Scott P. Leishmaniasis: complexity at the host-pathogen interface. Nat Rev Microbiol. 2011;9:604–15.
4. Silva Junior GB, Guardão Barros EJ, Daher EF. Kidney involvement in leishmaniasis – a review. Braz J Infect Dis. 2014;18:434–40.
5. Libório AB, Rocha NA, Oliveira MJC, et al. Acute kidney injury in children with visceral leishmaniasis. Pediatr Infect Dis J. 2012;31:451–4.
6. Oliveira MJC, Silva Junior GB, Abreu KL, et al. Risk factors for acute kidney injury in visceral leishmaniasis (Kala-Azar). Am J Trop Med Hyg. 2010;82:449–53.
7. Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. Clin Chem Lab Med. 2017;55:1074–89.
8. Ready PD. Epidemiology of visceral leishmaniasis. Clin Epidemiol. 2014;6:147–54.
9. Bern C, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. PLoS One. 2012;7:1–12.
10. Lindoso JA, et al. Visceral Leishmaniasis and HIV coinfection in Latin America. PLoS Negl Trop Dis. 2014;8:e3136.
11. Brasil. Ministério da Saúde. Situação Epidemiológica, leishmaniose visceral. Available at http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/svs/leishmaniose-visceral-lv. Accessed 1 August 2017.
12. Ceará, Secretaria de Saúde. Boletim Epidemiológico Leishmaniose Visceral; 2016. http://www.saude.ce.gov.br/index.php/boletins. Access August 2017.
13. Moriconi M, Rugna G, Calzolari M, et al. Phlebotomine sand fly–borne pathogens in the Mediterranean Basin: human leishmaniasis and phlebovirus infections. PLoS Negl Trop Dis. 2017;11(8):1–19.
14. Lestinova T, Rohousova I, Sima M, et al. Insights into the sand fly saliva: blood-feeding and immune interactions between sand flies, hosts, and Leishmania. PLoS Negl Trop Dis. 2017;11:1–26.
15. Dostálová A, Volf P. Leishmania development in sand flies: parasite-vector interactions overview. Parasit Vectors. 2012;5:276.
16. Rogers ME, Chance ML, Bates PA. The role of promastigote secretory gel in the origin and transmission of the infective stage of Leishmania mexicana by the sandfly Lutzomyia longipalpis. Parasitology. 2002;124:495–507.
17. Murray HW, Berman JD, Davies CR, et al. Advances in leishmaniasis. Lancet. 2005;366:1561–77.
18. McGwire BS, Satoskar R. Leishmaniasis: clinical syndromes and treatment. QJM. 2014;107:7–14.
19. Chappuis F, Sundar S, Hailu A, et al. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? Nat Rev Microbiol. 2007;5:873–82.
20. Daher EF, Lima LL, Vieira AP, et al. Hemophagocytic syndrome in children with visceral leishmaniasis. Pediatr Infect Dis J. 2015;34:1311–4.
21. Seaman J, Mercer AJ, Sondorp HE, et al. Epidemic visceral leishmaniasis in southern Sudan: treatment of severely debilitated patients under wartime conditions and with limited resources. Ann Intern Med. 1996;124:664–72.
22. Diro E, Lynen L, Gebregziabiher B, et al. Clinical aspects of paediatric visceral leishmaniasis in Northwest Ethiopia. Trop Med Int Heal. 2015;20:8–16.
23. Lafuse WP, Story R, Mahylis J, et al. Leishmania donovani infection induces anemia in hamsters by differentially altering erythropoiesis in bone marrow and spleen. PLoS One. 2013;8:1–12.
24. Daher EF, Soares DS, Filho SL, et al. Hyponatremia and risk factors for death in human visceral leish-

maniasis: new insights from a cross-sectional study in Brazil. BMC Infect Dis. 2017;17:168.
25. Al-Ghazaly J, Al-Dubai W. The clinical and biochemical characteristics of Yemeni adults and children with visceral leishmaniasis and the differences between them: a prospective cross- sectional study before and after treatment. Trop Dr. 2016;46:224–31.
26. Hag IA, Hashim FA, Toum IA, et al. Liver morphology and function in visceral leishmaniasis (Kala-azar). J Clin Pathol. 1994;47:547–51.
27. Khadem F, Gao X, Mou Z, et al. Hepatic stellate cells regulate liver immunity to visceral leishmaniasis through P110δ-dependent induction and expansion of regulatory T cells in mice. Hepatology. 2016;63:620–32.
28. Belo VS, Struchiner CJ, Barbosa DS, et al. Risk factors for adverse prognosis and death in American visceral leishmaniasis: a meta-analysis. PLoS Negl Trop Dis. 2014;8:1–9.
29. Ronet C, Hauyon-La Torre Y, Revaz-Breton M, et al. Regulatory B cells shape the development of Th2 immune responses in BALB/c mice infected with Leishmania major through IL-10 production. J Immunol. 2010;184:886–94.
30. Pastorino AC, Jacob CMA, Oselka GW, et al. Leishmaniose visceral: aspectos clínicos e laboratoriais Visceral leishmaniasis: clinical and laboratorial aspects. J Pediatr. 2002;78:120–7.
31. Brasil. Ministério da Saúde. Leishmaniose visceral: recomendações clinicas para redução da letalidade. Brasília: Ministério da Saúde; 2011.
32. Tajebe F, Getahun M, Adem E, et al. Disease severity in patients with visceral leishmaniasis is not altered by co-infection with intestinal parasites. PLoS Negl Trop Dis. 2017;11:5727.
33. World Health Organization. Control of the leishmaniases. World Health Organ Tech Rep Ser. 2010:22–6.
34. Rocha PN, Kobayashi CD, de Carvalho AL, et al. Incidence, predictors, and impact on hospital mortality of amphotericin B nephrotoxicity defined using newer acute kidney injury diagnostic criteria. Antimicrob Agents Chemother. 2015;59:4759–69.
35. Boelaert M, Rijai S, Regmi S, et al. A comparative study of the effectiveness of diagnostic tests for visceral leishmaniasis. Am J Trop Med Hyg. 2004;70:72–7.
36. Ho EA, Soong TH, Li Y. Comparative merits of sternum, spleen and liver punctures in the study of human visceral leishmaniasis. Trans R Soc Trop Med Hyg. 1948;41:629–36.
37. Zijlstra EE, Ali MS, el-Hassan AM, et al. Kala-azar: a comparative study of parasitological methods and the direct agglutination test in diagnosis. Trans R Soc Trop Med Hyg. 1992;86:505–7.
38. Reithinger R, Dujardin JC. Molecular diagnosis of leishmaniasis: current status and future applications. J Clin Microbiol. 2007;45:21–5.
39. Ruiter CM, et al. Molecular tools for diagnosis of visceral leishmaniasis: systematic review and meta-analysis of diagnostic test accuracy. J Clin Microbiol. 2014;52:3147–55.
40. Singh OP, Sundar S. Developments in diagnosis of visceral leishmaniasis in the elimination era. J Parasitol Res. 2015;2015:1–10.
41. Bern C, Adler-Moore J, Berenguer J, et al. Liposomal amphotericin B for the treatment of visceral leishmaniasis. Clin Infect Dis. 2006;43:917–24.
42. Rocha PN, Macedo MN, Kobayashi CD, et al. Role of urine neutrophil gelatinase-associated lipocalin (NGAL) in the early diagnosis of amphotericin B-induced acute kidney injury. Antimicrob Agents Chemother. 2015;59:6913–21.
43. Bates DW, Su L, Yu DT, et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. Clin Infect Dis. 2001;32:686–93.
44. Falci DR, Pasqualotto AC. Anfotericina B: uma revisão sobre suas diferentes formulações, efeitos adversos e toxicidade. Clin Biomed Res. 2015;35:65–82.
45. Mistro S, Maciel M, de Menezes RG, et al. Does lipid emulsion reduce amphotericin B nephrotoxicity? A systematic review and meta-analysis. Clin Infect Dis. 2012;54:1774–7.
46. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin b for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med. 1999;340:764–71.
47. Leenders AC, Daenen S, Jansen RL, et al. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. Br J Haematol. 1998;103:205–12.
48. Daher EF, Rocha NA, Oliveira MJ, et al. Renal function improvement with pentavalent antimonial agents in patients with visceral leishmaniasis. Am J Nephrol. 2011;33:332–6.
49. Salgado Filho N, Ferreira AF, Costa JML. Envolvimento da função renal em pacientes com leishmaniose visceral (Kala-azar). Rev Soc Bras Med Trop. 2003;36:217–21.
50. Sartori A, De Oliveira AV, Roque-Barreira MC, et al. Immune complex glomerulonephritis in experimental kala-azar. Parasite Immunol. 1987;9:93–103.
51. Daher EF, Evangelista LF, Silva Júnior GB, et al. Clinical presentation and renal evaluation of human visceral leishmaniasis (kala-azar): a retrospective study of 57 patients in Brazil. Braz J Infect Dis. 2008;12:329–32.
52. Lima Verde FAA, Daher EF, Dos Santos MG, et al. Renal tubular dysfunction in human visceral leishmaniasis (Kala-azar). Clin Nephrol. 2009;71:492–500.
53. Enriquez R, Sirvent AE, Padilla S, et al. Membranoproliferative glomerulonephritis due to visceral leishmaniasis in an HIV patient. Am J Case Rep. 2015;16:8–11.
54. Efstratiadis G, Boura E, Giamalis P, Mandala E, Leontsini M, Tsiaouisis G, Memmos D. Renal involvement in a patient with visceral leishmaniasis. Nephrol Dial Transplant. 2006;21:235–6.

55. Clementi A, Battaglia G, Floris M, et al. Renal involvement in leishmaniasis: a review of the literature. NDT Plus. 2011;4:147–52.
56. Elnojomi NA, Musa AM, Younis BM, et al. Surrogate markers of subtle kidney injury in patients with visceral leishmaniasis. Saudi J Kidney Dis Transpl. 2010;21:872–5.
57. Gorriz JL, Martinez-Castelao A. Proteinuria: detection and role in native renal disease progression. Transplant Rev (Orlando). 2012;26:3–13.
58. Alex S, Criado C, Fernández-Guerrero ML, de Górgolas M, et al. Nephrotic syndrome complicating chronic visceral leishmaniasis: re-emergence in patients with AIDS. Clin Nephrol. 2008;70:65–8.
59. Rocha NA, Oliveira MJ, Franco LF, et al. Comparative analysis of pediatric and adult visceral leishmaniasis in Brazil. Pediatr Infect Dis J. 2013;32:e182–5.
60. Parikh CR, Mansour SG. Perspective on clinical application of biomarkers in AKI. J Am Soc Nephrol. 2017;28:1677–85.
61. Wasung ME, Chawla LS, Madero M. Biomarkers of renal function, which and when? Clin Chim Acta. 2015;438:350–7.
62. Vaidya VS, Ferguson M, Bonventre JV. Biomarkers of acute kidney injury. Annu Rev Pharmacol Toxicol. 2008;48:463–93.
63. McCullough PA, Bouchard J, Waikar SS, et al. Implementation of novel biomarkers in the diagnosis, prognosis, and management of acute kidney injury: executive summary from the tenth consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. 2013;182:5–12.
64. Gonzales P, Pisitkun T, Knepper MA. Urinary exosomes: is there a future? Nephrol Dial Transplant. 2008;23:1799–801.
65. Mårtensson J, Martling CR, Bell M. Novel biomarkers of acute kidney injury and failure: clinical applicability. Br J Anaesth. 2012;109:843–50.
66. Parikh CR, Thiessen-Philbrook H, Garg AX, et al. Performance of kidney injury molecule-1 and liver fatty acid-binding protein and combined biomarkers of aki after cardiac surgery. Clin J Am Soc Nephrol. 2013;8:1079–88.
67. Ichimura T, Bonventre JV, Bailly V, et al. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J Biol Chem. 1998;273:4135–42.
68. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute kidney injury after cardiac surgery. Lancet. 2005;365:1231–8.
69. Haase M, Haase-Fielitz A. NGAL — from discovery to a new era of 'acute renal disease' diagnosis? Clin Biochem. 2011;44:499–500.
70. Kim MJ, Tam FWK. Urinary monocyte chemoattractant protein-1 in renal disease. Clin Chim Acta. 2011;412:2022–30.
71. Oliveira MJC, Silva Junior GB, Sampaio AM, et al. Preliminary study on tubuloglomerular dysfunction and evidence of renal inflammation in patients with visceral leishmaniasis. Am J Trop Med Hyg. 2014;91:908–11.
72. Meneses GC, De Francesco DE, da Silva Junior GB, Bezerra GF, da Rocha TP, de Azevedo IEP, Libório AB, Martins AMC. Visceral leishmaniasis-associated nephropathy in hospitalized Brazilian patients: new insights based on kidney injury biomarkers. Tropical Med Int Health. 2018;23:1046–57.
73. Kima PE, Soong L. Interferon gamma in leishmaniasis. Front Immunol. 2013;4:1–5.
74. Daher EF, Silva Junior GB. Nefropatia nas doenças tropicais. In: Riella MC, editor. Princípios de Nefrologia e Distúrbios Hidreletrolíticos. 6ª ed. Rio de Janeiro: Guanabara-Koogan; 2018. p. 553–81.

Malaria and Kidney Complications

25

Karla Cristina Silva Petruccelli, Valquir Silva dos Santos, Alba Regina Jorge Brandão, Izabella Picinin Safe Lacerda, Fernando Fonseca de Almeida e Val, and Marcus Vinícius Guimarães de Lacerda

25.1 Introduction

Human malaria is caused by species of the protozoan genus Plasmodium (*P. falciparum, P. vivax, P. ovale,* and *P. malariae*). The cycle begins with the inoculation of the parasite into humans during blood transfusions by female mosquitoes of the Anopheles genus. The disease is widespread globally, concentrated predominantly in tropical countries, and represents a major public health problem in these locations:. It is endemic in more than 90 countries on five continents and puts around 3.4 billion people at risk of infection [1, 2]. In 2022, the World Health Organization (WHO) estimates that there will be more than 249 million episodes, with a death toll of more than 608,000. The African continent accounts for 90% of malaria cases, with *P. falciparum* responsible for 99% of cases. In the other regions, *P. vivax* is the most prevalent parasite, accounting for 64% of cases in the Americas and 30% in Southeast Asia. In Brazil, for about a decade now, *P. vivax* has been responsible for about 85% of reported cases, mainly concentrated in the Amazon. Diagnosis is carried out by thick drop examination or rapid test.

K. C. S. Petruccelli (✉)
Department of Internal Medicine, Federal University of Amazonas, Manaus, Amazonas, Brazil

V. S. dos Santos · I. P. S. Lacerda
Division of Nephrology, Tropical Medicine Foundation Dr. Heitor Vieira Dourado, Manaus, Amazonas, Brazil

A. R. J. Brandão
Critical Care Unit, Getulio Vargas University Hospital, Federal University of Amazonas, Manaus, Amazonas, Brazil

F. F. de Almeida e Val
Critical Care Unit, Post-Graduation Program in Tropical Medicine, Tropical Medicine Foundation Dr. Heitor Vieira Dourado, Manaus, Amazonas, Brazil

M. V. G. de Lacerda
Post-Graduation Program in Tropical Medicine, Tropical Medicine Foundation Dr. Heitor Vieira Dourado, State University of Amazonas, Manaus, Amazonas, Brazil

25.2 Clinical Manifestations

Despite advances in malaria elimination and control strategies, recent WHO estimates still show high morbidity and mortality, especially when diagnosis is delayed, which is often the case in less endemic areas [2]. Malaria affects people of all age groups, with a broad clinical spectrum ranging from asymptomatic infection to death. The development of clinical complications in malaria is due to the systemic involvement of the disease, which can contribute to acute kidney injury (AKI).

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_25

25.3 Acute Kidney Injury in Malaria

The WHO classifies renal dysfunction as a complication in malaria when serum creatinine levels exceed 3.0 mg/dL [3]. This classification standard is different and less sensitive than the RIFLE (Risk, Injury, Failure, Loss, and End-stage Renal Disease), AKIN (Acute Kidney Injury Network), and KDIGO (Kidney Disease Improving Outcomes) scales, which may mean that cases of Acute Kidney Injury are underreported in several series of records [4].

AKI in malaria has a higher prevalence in older age groups, being reported in up to 40% of severe cases of *P. falciparum* infection in adults [5–7]. In areas endemic for *P. vivax*, it is estimated that 16% develop this complication [8]. One study analyzed 288 monoinfected patients with *P. falciparum* (191) and *P. vivax* (97) malaria and concluded that despite the higher prevalence of AKI in *P. falciparum*, *P. vivax* malaria can also cause kidney injury of similar severity [9]. Malaria caused by *P. malariae*, although rare, can also develop kidney complications [10, 11]. In tropical areas, malaria is always an etiological diagnosis to be considered in AKI in patients with acute febrile syndrome, with leptospirosis, hantavirus, yellow fever, dengue, and sepsis as differential hypotheses.

The clinical manifestations of AKI are mainly oligoanuria, severe metabolic acidosis, hypercatabolic state, and hydroelectrolytic disorders such as hyponatremia and hyperkalemia [6]. Several factors are considered risk factors for the development of AKI secondary to malaria, the main ones being the patient's advanced age, hyperkalemia, liver dysfunction with hyperbilirubinemia, use of vasoactive drugs, leukocytosis, and sepsis due to secondary bacterial infections [6]. In addition, factors related to hemodynamics (hypovolemia), vascular (intravascular hemolysis, central and peripheral vasoconstriction and changes in microcirculation), cell destruction (hemolysis and hemoglobinuria), malaria (high parasitemia), and the immune response (deposition of immune complexes) also contribute to the occurrence of kidney injury [5, 6, 8, 12, 13]. It is not uncommon in malaria to find sterile pyuria (mild or moderate) on urine sediment analysis, which can mistakenly confuse the diagnosis of acute febrile syndrome with urinary tract infection, leading to the unnecessary use of antimicrobials, some of which can reduce malarial parasitemia, such as sulfas, clindamycin, and quinolones, making early parasitological diagnosis difficult. Urinary tract infection can eventually be a complication in patients who have undergone delayed bladder catheterization after being admitted to an intensive care unit due to other clinical complications.

The pathogenesis of AKI in malaria needs to be better understood, but it is clear that it is a multifactorial process. The hemodynamic changes resulting from the sequestration of erythrocytes by the formation of hematic rosettes in large vascular beds result in a deficit in microcirculation, which can lead to tissue hypoxia, which, together with the endothelial damage caused by cytoadherence, is a risk factor for acute tubular necrosis. Another important component of this hypovolemia process is the dehydration constantly associated with severe malaria. However, immunological phenomena cannot be excluded from this cascade, since there is abundant production of pro-inflammatory cytokines (TNF-α and interleukins 1, 6, 8, and γ) and eventual deposition of immune complexes, producing interstitial nephritis and glomerulonephritis. Also to be taken into account is the metabolic disruption, which ends up increasing the production of prostaglandins with a potential vasoconstrictor effect [4, 14, 15].

The presence of new markers of kidney injury has been investigated in *P. falciparum* malaria, particularly NGAL (neutrophil gelatinase-associated lipocalin) and KIM-1 (Kidney injury molecule 1), which are earlier markers of kidney dysfunction, preceding changes in serum creatinine levels [5]. High levels of NGAL are an independent risk factor for progression to Acute Kidney Disease (AKD) and mortality in children with malaria [16].

25.4 Glomerulopathies in Malaria

25.4.1 Glomerular Lesion Associated with Plasmodium Falciparum

The clinical presentation of glomerular lesions associated with *P. falciparum* is varied, and they are perhaps underdiagnosed due to the fact that they are involved in the context of an infectious process that can present severe multi-organ involvement. Children infected with *P. falciparum* can have an incidence of asymptomatic proteinuria of up to 81%. Most series report an incidence of mild proteinuria, micro hematuria and the presence of hematic cylinders in 20 to 50% of infected patients [17].

Glomerulopathy associated with *P. falciparum* can induce nephrotic or nephritic conditions, but hypertension is uncommon. Complement is generally consumed and the most prevalent forms are reversible, between 2 and 6 weeks after the parasitemia clears [14].

The most frequently found lesion is mesangial proliferation. Expansion of the mesangial matrix is discreet and alterations to the glomerular basement membrane are not common. Deposits of granular eosinophilic material can be found on the walls of the capillaries, in the mesangium and in Bowman's capsule. Immunofluorescence shows granular deposits of IgM and C3 in the capillaries and mesangium. Malarial antigens are usually found in the glomerular endothelium and medullary capillaries. Electron microscopy shows subendothelial and mesangial electron-dense deposits together with granular, fibrillar, and amorphous material. Tubular alterations include cellular edema, granular deposits of hemosiderin, and varying degrees of necrosis. The interstitium is edematous, with a mononuclear cell infiltrate of varying degrees. Parasitized erythrocytes are commonly found. The mechanism of this lesion is mediated by immune complexes. Immunosuppression should be avoided in these lesions, with treatment limited to effective antimalarial therapy and clinical support measures [14, 18].

A less frequent form of lesion is collapsing segmental and focal glomerulosclerosis (FSGS) with a nonimmune pattern [19]. Unlike the immune-mediated lesion, the collapsing FSGS of *P. falciparum* infection manifests as nephrotic syndrome and can evolve with accelerated kidney functional loss, especially since it is often superimposed on malaria AKI, even determining the need for dialysis. This form of collapsing FSGS, which seems to be more prevalent among black individuals of African origin, can have a variable course, ranging from complete remission to end-stage renal disease. There is no evidence of which factors have a poor prognosis, but delaying the start of antimalarial therapy seems to be one of the determinants of a worse outcome. There are reports of better results when pulse therapy with corticosteroids or immunosuppressants is combined with antimalarial therapy [20]. The presence of high-risk variables in the APOL1 gene seems to be associated with a higher risk of collapsing FSGS in populations of African origin [21].

Another important condition is secondary hemophagocytic syndrome (HPS), which can lead to acute kidney injury and nephrotic syndrome [22]. HPS, also known as macrophage activation syndrome, is characterized by massive infiltration of the bone marrow and lymphoid organs by activated macrophages originating from a hyperinflammatory state. Subsequent acute kidney injury and tubular necrosis are consequences of the high levels of cytokines. The glomerular lesions most frequently found in HPS are collapsing glomerulosclerosis and minimal lesion disease [22, 23]. Rarely, thrombotic microangiopathy may occur. Very high levels of TNF-α, such as those seen in HPS, can disorganize the cytoskeleton of podocytes and increase glomerular permeability to albumin. Individuals of African origin seem to be subject to more severe forms of collapsing lesions. Antimalarial treatment with the consequent elimination of the factor triggering HPS is the most important element of treatment. Corticosteroids, cyclosporine, and biological agents such as rituximab should also be evaluated, as well as intravenous immunoglobulin [22].

25.4.2 Glomerular Damage Associated with Plasmodium Malariae

The first descriptions of nephrotic conditions associated with *P. malariae* are mainly of African origin, and in the 1960s and 1970s accounted for 80% of cases of secondary nephrotic syndrome [24]. However, there has been a significant reduction in this condition in recent decades, most likely due to greater access to health services [17].

Nephropathy associated with malaria caused by *P. malariae* is a lesion that leads to proteinuria, of a chronic nature, which preferentially affects children and begins a few weeks after infection. It is a lesion mediated by immune complexes, which generally does not respond to antimalarial therapy alone. Although there are reports of spontaneous remission in the milder forms, what is most often observed is a poor response to corticotherapy and other forms of immunosuppression, with a high potential for progression to chronic kidney disease over a period of 3–5 years [14, 18].

Pathological findings on light microscopy include segmental thickening of the glomerular capillaries in chronic forms of membranous-proliferative glomerulonephritis, produced by the subendothelial deposition of Periodic Acid-Schiff (PAS)-positive argyrophilic fibrils in a plexiform arrangement; double contour, with obliteration of the glomerular capillaries and eventual formation of crescents and tubular atrophy and lymphomononuclear infiltrate in the endothelial compartment [25]. Immunofluorescence reveals deposits of IgG, IgM, C3, and rarely IgA in the mesangium and subendothelial space. Electron microscopy reveals lacunae of electron-dense material with a density similar to that of the basement membrane [18, 25].

25.4.3 Glomerular Lesion Associated with Plasmodium Vivax

Sporadic case reports have shown that postinfectious glomerulonephritis (PIG) is the most commonly described form of glomerulopathy and presents as a nephritic syndrome and transient hypocomplementemia, which can be benign [26, 27], or with severe progression and the need for dialysis [28]. It can also present with normal complement levels, and is more common in children [29]. Other forms of glomerulopathy are membranoproliferative glomerulonephritis and crescentic glomerulonephritis [30]. Symptoms of nephrotic syndrome are rare and are usually corticoid-resistant. The most common histological lesion in these cases is pure mesangial proliferation, and children are more frequently affected, with reports of congenital forms of nephrotic syndrome [31, 32].

Thrombotic microangiopathies (MAT) can also occur, but more rarely. MAT associated with malaria occurs with normal levels of complement fractions. Histopathological findings, in addition to those compatible with thrombotic microangiopathy, include concomitant interstitial nephritis, with infiltrates of lymphocytes, plasma cells, and eosinophils. In cases of MAT, early indication for plasmapheresis is recommended, in addition to antimalarial therapy. There is a potential for progression to end-stage renal disease [33, 34].

The mechanisms of glomerular damage associated with *P. vivax* have not yet been fully clarified. A high prevalence of antineutrophil cytoplasmic antibodies (ANCA) and anti-cathepsin G has been found in populations with acute malaria, even in the absence of vasculitis, indicating neutrophil activation, which could induce an imbalance in the production of pro-inflammatory cytokines, triggering a hyperimmune response and subsequent glomerular injury [35]. Hyperparasitemia also plays an important role, since there is an increase in the cytoadherence of parasitized erythrocytes to the vascular endothelium [36]. The infection would imply a reduction in the levels of ADAMTS 13 (disintegrin and metalloprotease with thrombospondin 1-like domain), which would result in a reduction in the cleavage of the von Willebrand factor [37]. Microangiopathies are also associated with increased levels of thrombomodulin, ICAM-1, E-selectin, and VCAM-1 in the acute phases of *P. vivax* infection [38]. Reduced serum

levels of IL-10 are associated with crescent formation, and this cytokine plays a well-established role in attenuating crescentic glomerulonephritis [39, 40].

25.5 Hydroelectrolytic Changes in Malaria

Patients with malaria may experience variations in volemia, depending on the stage and evolution of the infection and kidney damage. Increased vascular permeability in the face of a hyperinflammatory state, secondary to the disease and kidney damage, can lead to loss of volume in the intravascular space and consequent hypovolemia and reduced cardiac output. With a reduction in the glomerular filtration rate, increased secretion of ADH, and stimulation of baroceptors, there is an increase in tubular reabsorption of water and sodium, causing hypervolemia and an increase in urine output [41, 42].

Patients with malaria may show a deficient adaptive response to sudden volume changes and water overload when they are severely ill. Changes in sodium and water transport in the pulmonary alveolar epithelium, for example, due to alterations in the regulation and expression of aquaporin sodium channels, may imply an increased risk of respiratory distress syndrome in patients with severe malaria, which requires careful control of water intake in these patients, as well as the rational use of loop diuretics [41]. Artesunate, a derivative of artemisinin, an important antimalarial for the treatment of severe malaria, induces natriuresis by reducing NKCC2-mediated transport at the tubular level [43], which can help to reduce hypervolemia.

The main electrolyte alteration is hyponatremia, which can be seen in up to 67% of patients [14], is generally asymptomatic and resolves in a large proportion of cases with specific treatment of the disease. However, when symptomatic, it is a warning sign of other serious complications of malaria such as adrenal insufficiency and cerebral malaria. Hypernatremia is not common, but when it is present, it is indicative of a poor prognosis and may mean hypothalamic lesions. Hypokalemia, common in febrile illnesses, can occur in up to 40% of individuals with malaria [44]. Hyperkalemia is less frequent and is usually associated with serious complications of malaria, such as rhabdomyolysis or primaquine-induced hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, an enzyme deficiency linked to the X chromosome. Hypocalcemia can be observed in up to 45% of patients with severe malaria and can be an indicator of poor prognosis [45, 46].

25.6 Acute Kidney Injury Secondary to Antimalarial Treatment

In cases of *P. vivax* malaria, radical treatment should be with chloroquine (which eliminates the blood forms) and primaquine (the only medication available to treat hepatic hypnozoites, which are responsible for relapses). Primaquine, when used in patients with G6PD deficiency, which represents around 4.5% of the male population in the Brazilian Amazon, can trigger methemoglobinemia and hemolysis, due to excess oxidative stress. The problem is more frequent in men (XY) because the genetic deficiency is linked to the X chromosome (men are hemizygous), whereas women (XX) need to have two deficient chromosomes (homozygous) or absence of lyonization of the defective chromosome in order to present the deficiency phenotype. Hemolysis often occurs on the second or third day of primaquine use, and its intensity depends in part on: type of deficiency (severe deficiency is assumed to be enzyme activity of less than 10%), high parasitemia, hyperthermia, and primaquine dose. In addition to severe anemia, the most feared complication in these cases is AKI, which can set in abruptly due to the accumulation of hemoglobin in the renal tubules (Fig. 25.1). These complications of primaquine use are rarely reported, because in general the presence of anemia, jaundice, and choluria after the start of treatment is associated with malaria infection per se, or mistakenly referred to by the affected population as "post-malaria hepatitis". As the non-severe con-

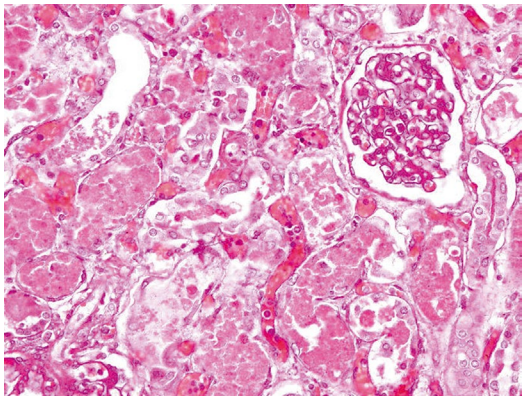


Fig. 25.1 Optical microscopy (1000×) showing acute tubular necrosis and tubular hemoglobin cylinders in a male patient with undiagnosed G6PD deficiency after treatment for vivax malaria with chloroquine and primaquine, who died after massive hemolysis and AKI with no response to dialysis treatment

dition is self-limiting, due to the compensation of the G6PD deficiency with the release of more reticulocytes by the bone marrow, little importance is given to the milder cases, which are underreported. It is believed that other antihypnozoite drugs, such as tafenoquine (derived from primaquine, but with a longer half-life, which allows treatment in a single dose), have a similar complication in G6PD deficients. Routinely, no endemic country screens for G6PD deficiency prior to primaquine treatment. However, the presence of diabetes mellitus, family history or previous history of hemolysis after primaquine use should raise suspicion and the test should be carried out, when available.

25.7 Treatment

In the therapeutic approach, the following are still important risk factors for all the complications mentioned: primoinfection, prolonged illness, and hyperparasitemia [64]. An important fact to mention is the change in the causative agent of the most significant cases of kidney involvement in Brazil in recent decades. In three consecutive periods, 1977 to 1983, 1984 to 1989, and 1990 to 1995, there were, respectively, 89, 91, and 70 cases of malaria with creatinine greater than 3.0 mg/dL, admitted to a reference institution in Manaus. All cases were related to *P. falciparum*68. From 2013 to 2017, ten patients with a diagnosis of malaria were dialyzed, eight of them with a diagnosis of *P. vivax*, with and without post-primaquine hemolysis (unpublished data).

The treatment of kidney dysfunction associated with malaria involves not only the appropriate use of antimalarial therapy for the infection, which is a cornerstone in the approach to these patients, but also patient support measures (signs of severity, hypovolemia, and metabolic dysfunctions) and reversal of the kidney condition, with correction of hydroelectrolytic disorders, fluid replacement, and, if necessary, dialysis [10, 47].

Malaria treatment varies according to the infecting species, clinical manifestations, severity classification, weight, pregnancy, and local resistance profile to antimalarials. Early diagnosis and timely treatment are still considered the most appropriate means of reducing the onset of complications and the lethality of the disease [48].

Malaria treatment in Brazil is available to the entire population through the public health system and through a positive diagnostic test performed at different levels of care. In the case of vivax malaria, treatment involves a combination of chloroquine (a total of 25 mg/kg of body weight, divided into 3 days) and primaquine (0.25 mg/kg of body weight for 14 days) [49]. However, in Brazil and some other Latin American countries, primaquine is used in a short regimen for 7 days (0.5 mg/kg/day), due to low adherence by the population to the long regimen [50, 51]. In these cases, if patients have African-type G6PD deficiency (A−), increasing the daily dose of primaquine may be associated with a higher risk of developing severe hemolysis with AKI. Another alternative for achieving a radical cure for *P. vivax* malaria in individuals with normal G6PD activity is tafenoquine in a single dose of 300 mg as an alternative to longer regimens using primaquine [52]. In the case of falciparum malaria, the use of some ACT (Artemisinin-Combined Therapy) is recommended. In Brazil, artemether-lumefantrine is used for 3 days, with

a single dose of primaquine as a gametocytocidal [53]. In this case, the low dose of primaquine does not have a great potential to induce hemolysis in G6PD-deficient individuals.

Patients with malaria are almost all dehydrated and hypovolemic, which increases the risk of lactic acidosis and AKI, which are important prognostic factors for the disease [54, 55]. However, although volume replacement is one of the main measures adopted in these cases, it should be used with caution in this patient population. Factors such as microvascular obstruction by infected erythrocytes, inflammatory cells, and high vascular permeability can lead, for example, to the development of pulmonary edema, which is generally fatal if aggressive volume replacement is instituted [56, 57]. Therefore, even in cases of dehydration and fluid and electrolyte changes, volume correction should be performed with caution, especially in patients with severe malaria [58]. The suggestion is that volumes should not exceed 25 mL/kg/day.

In cases of post-primaquine hemolysis, the use of sodium bicarbonate to alkalinize urine and thus prevent AKI has no proven evidence and is therefore not routinely performed. Increased fluid intake, however, is a protective factor, but always taking into account the possibility of pulmonary edema, since there is almost always inflammation of the pulmonary vascular endothelium.

Dialysis should be considered for the treatment of AKI, with hemodialysis being more effective. It has become an important modality for reversing these disorders and has shown positive results in the treatment of kidney injury in these patients [48]. The procedure has been shown to be necessary in up to 75% of malaria cases, with complete recovery in more than 60% of cases [59]. In centers where renal support is available, early initiation of dialysis has been able to reduce mortality by 25% compared to those with late initiation [60–62].

Dialysis indications for this population follow stage 3 of the RIFLE or AKIN scales, especially in the criterion related to diuresis—urine output less than 0.3 mL/kg/h in 24 h or anuria in 12 h. Higher creatinine values, but with diuresis present, and without additional severity factors such as comorbidities in patients with prolonged disease, tend to have recovery of kidney function with specific antimalarial therapy and parsimonious hydration. Critically ill patients with hemodynamic instability and respiratory failure requiring mechanical ventilation should start renal replacement therapy early.

The most commonly used method is conventional or intermittent hemodialysis for hemodynamically stable patients, and extended daily dialysis for unstable patients, with migration between methods possible depending on clinical evolution.

Regarding anticoagulation, during dialysis treatment, it is essential to pay attention to laboratory alterations, which anticipate possible hemorrhagic complications and should guide the prescription. Platelet counts below 100,000/mm^3, changes in TAP/INR, and possible active bleeding contraindicate the use of anticoagulants. Such scenarios are more frequent in the first sessions, when there are still higher parasitemias. In these situations, we opt for heparin-free dialysis, in which the extracorporeal circuit is rinsed with saline solution containing only 3000–5000 IU of heparin/L, which can coat the internal surface of the circuit and the dialyzer membrane to minimize the thrombogenic response [69]. In cases with more severe hemorrhagic disorders, the option is to completely suspend any anticoagulant. In both situations, the circuit is bathed with 0.9% saline solution (100 mL every 30 min), and this volume must be removed during the session itself.

To obtain vascular access for dialysis, it is also important to evaluate the coagulogram, with the order of preference suggested by KDIGO: right jugular vein, then femoral vein. The jugular vein option, preferably guided by ultrasound, with thrombocytopenia may predispose to serious complications. The femoral vein is a good alternative due to its simplicity, especially in less experienced operators, abolishing the risks of hemothorax, pneumothorax, and injury to the central nervous plexuses. Originally, it was believed that the femoral approach presented a greater risk of infection, but there is

recent evidence of comparable infection rates and catheter tip colonization in femoral and jugular sites.

The pharmacokinetics of some antimalarials, such as chloroquine, are affected in patients with kidney injury. The same does not occur, for example, with mefloquine, atovaquone, and doxycycline, drugs used in various parts of the world for malaria prophylaxis [63]. However, in cases of AKI, which characterize the diagnosis of severe malaria, the option should always be the use of injectable artemisinin derivatives, even in the case of *P. vivax* infection.

Early diagnosis of malaria and kidney disorders, together with timely therapy, enable a better prognosis and reduced mortality [61, 64].

References

1. Sachs J, Malaney P. The economic and social burden of malaria. Nature. 2002;415(6872):680–5.
2. WHO - World Health Organization. World Malaria Report; 2017.
3. WHO | Severe malaria. WHO - Trop Med Int Heal 19, Suppl 1 (November 2014). 2014;125.
4. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1.
5. Koopmans LC, Van Wolfswinkel ME, Hesselink DA, Hoorn EJ, Koelewijn R, Van Hellemond JJ, et al. Acute kidney injury in imported plasmodium falciparum malaria. Malar J. 2015;14(1):1–7.
6. Win KKYK, Thanachartwet V, Wattanagoon Y, Jerraksuwan S, Ruangweerayut R, Desakorn V. Factors associated with acute renal failure in adults with severe falciparum malaria. Southeast Asian J Trop Med Public Health. 2012;43(5):1071–9.
7. Conroy AL, Hawkes M, Elphinstone RE, Morgan C, Hermann L, Barker KR, et al. Acute kidney injury is common in pediatric severe malaria and is associated with increased mortality. Open Forum Infect Dis. 2016;3(2):1–9.
8. Naqvi R. Plasmodium vivax causing acute kidney injury: a foe less addressed. Pak J Med Sci. 2015;31(6):1472–5.
9. Nayak KC, Kumar S, Gupta BK, Kumar S, Gupta A, Prakash P, et al. Clinical and histopathological profile of acute renal failure caused by falciparum and vivax monoinfection: an observational study from Bikaner, northwest zone of Rajasthan, India. J Vector Borne Dis. 2014;51(1):40–6.
10. Da Silva Junior GB, Pinto JR, Barros EJG, Farias GMN, Daher EDF. Kidney involvement in malaria: an update. Rev Inst Med Trop Sao Paulo. 2017;59(February):1–6.
11. Badiane AS, Diongue K, Diallo S, Ndongo AA, Diedhiou CK, Deme AB, et al. Acute kidney injury associated with Plasmodium malariae infection. Malar J. 2014;13:226.
12. Kute VB, Trivedi HL, Vanikar AV, Shah PR, Gumber MR, Patel HV, et al. Plasmodium vivax malaria-associated acute kidney injury, India, 2010–2011. Emerg Infect Dis. 2012;18(5):842–5.
13. Saravu K, Rishikesh K, Parikh CR. Risk factors and outcomes stratified by severity of acute kidney injury in malaria. PLoS One. 2014;9(3):e90419.
14. Barsoum R, Fayad T, Praditpornsilpa K, Sitprija V. Tropical nephrology. In: Coffman T, Falk R, Molitoris B, Neilson E, Schrier R, editors. Schrier's diseases of the kidney. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. p. 1800–44.
15. Brown DD, Solomon S, Lerner D, Del Rio M. Malaria and acute kidney injury. Pediatr Nephrol. 2020;35(4):603–8.
16. Namazzi R, Batte A, Opoka RO, Bangirana P, Schwaderer AL, Berrens Z, et al. Acute kidney injury, persistent kidney disease, and post-discharge morbidity and mortality in severe malaria in children: a prospective cohort study. EClinicalMedicine. 2022;44:101292.
17. Olowu WA, Ademola A, Ajite AB, Saad YM. Childhood nephrotic syndrome in tropical Africa: then and now. Paediatr Int Child Health. 2017;37(4):259–68.
18. Elsheikha HM, Sheashaa HA. Epidemiology, pathophysiology, management and outcome of renal dysfunction associated with plasmodia infection. Parasitol Res. 2007;101(5):1183–90.
19. Sehar N, Gobran E, Elsayegh S. Collapsing focal segmental Glomerulosclerosis in a patient with acute malaria. Case Rep Med. 2015;2015:420459.
20. van Wolfswinkel ME, van Genderen PJJ, Goemaere NNT, van Alphen AM. Collapsing glomerulopathy after Plasmodium falciparum infection. Clin Kidney J. 2014;7(5):495–6.
21. Amoura A, Moktefi A, Halfon M, Karras A, Rafat C, Gibier JB, et al. Malaria, collapsing glomerulopathy, and focal and segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2020;15(7):964–72.
22. Esmaili H, Mostafidi E, Mehramuz B, Ardalan M, Mohajel-Shoja M. An update on renal involvement in hemophagocytic syndrome (macrophage activation syndrome). J Nephropathol. 2016;5(1):8–14.
23. Niang A, Niang SE, Ka EHF, Ka MM, Diouf B. Collapsing glomerulopathy and haemophagocytic syndrome related to malaria: a case report. Nephrol Dial Transplant. 2008;23(10):3359–61.
24. Hendrickse RG, Adeniyi A. Quartan malarial nephrotic syndrome in children. Kidney Int. 1979;16(1):64–74.
25. Sinniah R, Churg J, Sobin L. Renal involvement in tropical diseases. Chicago: ASCP; 1988.

26. Zaki SA, Shanbag P. Acute glomerulonephritis: an unusual manifestation of Plasmodium vivax malaria. Ann Trop Paediatr. 2011;31(2):181–4.
27. Zaki SA, Shanbag P. Plasmodium vivax with acute glomerulonephritis in an 8- year old–queries. J Vector Borne Dis. 2010;47(4):264. author reply 264
28. Kanodia KV, Vanikar AV, Kute VB, Trivedi HL. Plasmodium vivax malaria associated with acute post infectious glomerulonephritis. Ren Fail. 2013;35(7):1024–6.
29. Bhatt GC, Nandan D, Dewan V, Dey S. Plasmodium vivax presenting as acute glomerulonephritis in a 3-year-old child. Trop Dr. 2012;42(1):63–4.
30. Patel MP, Kute VB, Gumber MR, Gera DN, Shah PR, Patel HV, et al. An unusual case of Plasmodium vivax malaria monoinfection associated with crescentic glomerulonephritis: a need for vigilance. Parasitol Res. 2013;112(1):427–30.
31. David J, Shanbag P, More V. Plasmodium vivax malaria presenting as the nephrotic syndrome in an infant. Trop Dr. 2009;39(2):127–8.
32. Bircan Z, Kervancioğlu M, Soran M, Gönlüşen G, Tuncer I. Two cases of nephrotic syndrome and tertian malaria in South-Eastern Anatolia. Pediatr Nephrol. 1997;11(1):78–9.
33. Sinha A, Singh G, Bhat AS, Mohapatra S, Gulati A, Hari P, et al. Thrombotic microangiopathy and acute kidney injury following vivax malaria. Clin Exp Nephrol. 2013;17(1):66–72.
34. Jhorawat R, Beniwal P, Malhotra V. Plasmodium vivax induced hemolytic uremic syndrome: an uncommon manifestation that leads to a grave complication and treated successfully with renal transplantation. Trop Parasitol. 2015;5(2):127–9.
35. Yahya TM, Benedict S, Shalabi A, Bayoumi R. Antineutrophil cytoplasmic antibody (ANCA) in malaria is directed against cathepsin G. Clin Exp Immunol. 1997;110(1):41–4.
36. Carvalho BO, Lopes SCP, Nogueira PA, Orlandi PP, Bargieri DY, Blanco YC, et al. On the cytoadhesion of Plasmodium vivax-infected erythrocytes. J Infect Dis. 2010;202(4):638–47.
37. de Mast Q, Groot E, Asih PB, Syafruddin D, Oosting M, Sebastian S, et al. ADAMTS13 deficiency with elevated levels of ultra-large and active von Willebrand factor in P. falciparum and P. vivax malaria. Am J Trop Med Hyg. 2009;80(3):492–8.
38. Ohnishi K. Serum levels of thrombomodulin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin in the acute phase of Plasmodium vivax malaria. Am J Trop Med Hyg. 1999;60(2):248–50.
39. Sinniah R, Rui-Mei L, Kara A. Up-regulation of cytokines in glomerulonephritis associated with murine malaria infection. Int J Exp Pathol. 1999;80(2):87–95.
40. Kitching AR, Tipping PG, Huang XR, Mutch DA, Holdsworth SR. Interleukin-4 and interleukin-10 attenuate established crescentic glomerulonephritis in mice. Kidney Int. 1997;52(1):52–9.
41. Sitprija V. Altered fluid, electrolyte and mineral status in tropical disease, with an emphasis on malaria and leptospirosis. Nat Clin Pract Nephrol. 2008;4(2):91–101.
42. Sitprija V, Napathorn S, Laorpatanaskul S, Suithichaiyakul T, Moollaor P, Suwangool P, et al. Renal and systemic hemodynamics, in falciparum malaria. Am J Nephrol. 1996;16(6):513–9.
43. Campos SB, Rouch LH, Seguro AC. Effects of sodium artesunate, a new antimalarial drug, on renal function. Kidney Int. 2001;59(3):1044–51.
44. Maitland K, Pamba A, Newton CRJC, Lowe B, Levin M. Hypokalemia in children with severe falciparum malaria. Pediatr Crit Care Med. 2004;5(1):81–5.
45. Prabha MR, Pereira P, Chowta N, Hegde BM. Clinical implications of hypocalcemia in malaria. Indian J Med Res. 1998;108:62–5.
46. Soni CL, Kumhar MR, Gupta BK, Singh VB, Srimali L, Nayak KC, et al. Prognostic implication of hypocalcemia and QTc interval in malaria. Indian J Malariol. 2000;37(3–4):61–7.
47. Kute V, Munjappa B, Patel H, Engineer D, Vanikar A, Shah P, et al. Outcome and prognostic factors of malaria-associated acute kidney injury requiring hemodialysis: a single center experience. Indian J Nephrol. 2012;22(1):33.
48. World Health Organization. Guidelines for the treatment of malaria; 2015.
49. WHO. Guidelines for the treatment of malaria. 2nd ed. Geneva, Switzerland; 2010.
50. Pereira EA, Ishikawa EAY, Fontes CJF. Adherence to Plasmodium vivax malaria treatment in the Brazilian Amazon Region. Malar J. 2011;10:355.
51. Grietens KP, Soto V, Erhart A, Ribera JM, Toomer E, Tenorio A, et al. Adherence to 7-day primaquine treatment for the radical cure of P. vivax in the Peruvian Amazon. Am J Trop Med Hyg. 2010;82(6):1017–23.
52. Lacerda MVG, Llanos-Cuentas A, Krudsood S, Lon C, Saunders DL, Mohammed R, et al. Single-dose Tafenoquine to prevent relapse of plasmodium vivax malaria. N Engl J Med. 2019;380(3):215–28.
53. Silva AR da, Espinosa FEM, Souza JM de, Boulos M, Alecrim M das GC, Pereira M da PL, et al. Guia prático de tratamento da malária no Brasil: Ministério da Saúde – Brasil; 2010.
54. Hanson J, Lee SJ, Mohanty S, Faiz MA, Anstey NM, Charunwatthana P, et al. A simple score to predict the outcome of severe malaria in adults. Clin Infect Dis. 2010;50(5):679–85.
55. Bruneel F, Tubach F, Corne P, Megarbane B, Mira J-P, Peytel E, et al. Severe imported falciparum malaria: a cohort study in 400 critically ill adults. Sinnis P, editor. PLoS One. 2010;5(10):e13236.
56. White NJ, Turner GDH, Day NPJ, Dondorp AM. Lethal malaria: Marchiafava and Bignami were right. J Infect Dis. 2013;208(2):192–8.
57. Taylor WRJ, Hanson J, Turner GDH, White NJ, Dondorp AM. Respiratory manifestations of malaria. Chest. 2012;142:492–505.

58. Hanson J, Anstey NM, Bihari D, White NJ, Day NP, Dondorp AM. The fluid management of adults with severe malaria. Crit Care. 2014;18(6)
59. Naqvi R, Akhtar F, Ahmed E, Sheikh R, Bhatti S, Haider A, et al. Malarial acute kidney injury: 25 years experience from a Center in an Endemic Region. Br J Med Med Res. 2016;12(6):1–6.
60. Trang TT, Phu NH, Vinh H, Hien TT, Cuong BM, Chau TT, et al. Acute renal failure in patients with severe falciparum malaria. Clin Infect Dis. 1992;15(5):874–80.
61. Goyal MK, Yadav Y, Sharma L, Yadav K. A study of correlation between hepatic and renal dysfunction in malarial patients in Rajasthan. India Int J Contemp Paediatr. 2016;3(4):1278–83.
62. Wang C, Lv L-S, Huang H, Guan J, Ye Z, Li S, et al. Initiation time of renal replacement therapy on patients with acute kidney injury: a systematic review and meta-analysis of 8179 participants. Nephrology. 2017;22(1):7–18.
63. Amet S, Zimner-Rapuch S, Launay-Vacher V, Janus N, Deray G. Malaria prophylaxis in patients with renal impairment. Drug Saf. 2013;36(2):83–91.
64. Mehta KS, Halankar AR, Makwana PD, Torane PP, Satija PS, Shah VB. Severe acute renal failure in malaria. J Postgrad Med. 2001;47(1):24–6.

Part VI

Kidney Diseases Associated with Bacteria

26 Post-streptococcal and Epidemic Glomerulonephritis

Artur Quintiliano Bezerra da Silva
and Gianna Mastroianni Kirsztajn

26.1 Introduction

The main example of postinfectious glomerulonephritis (PIG) are the glomerular lesions described after a pharyngeal or cutaneous streptococcal infection and which do not represent the clinical or immunological pattern observed, for example, in a virus-associated PIG [1].

Post-streptococcal GN (PEGN) is an immunologically mediated glomerulopathy triggered by a previous streptococcal infection with nephritogenic strains of group A beta-hemolytic streptococcus. The latency time between infection and the development of glomerulonephritis would be the period necessary for streptococcal antigens to induce antibody synthesis, followed by the formation and deposition of soluble immune complexes, with complement activation and consumption [2].

26.2 Epidemiology

Since Bright's [3] description of acute postinfectious glomerulonephritis or acute diffuse glomerulonephritis (ADG) in 1836, one of the earliest observations in nephrology, numerous epidemics of the disease have occurred in various regions of the world. The true incidence of postinfectious GN is difficult to determine, as it is underreported and unrecognized due to its transient nature. The worldwide incidence of GNDA due to streptococcal infection is estimated at 472,000 cases/year, with children accounting for 86% of these cases and more than 96% occurring in developing countries. Subclinical postinfectious GN is expected to occur 4–19 times more frequently than symptomatic disease and may account for up to half of cases globally. The incidence varies in industrialized versus emerging countries or undeveloped (aboriginal) communities, and 28.5 cases per 100,000 people have been reported in developing nations [4]. Men have a risk twice as high as women. Climate influences the development of GNDA, with a higher incidence in the tropics. This situation is multifactorial and related to a richer "bio-ecological" environment, with a greater possibility of infection. Under these circumstances, epidemics are cyclical and occur at intervals of 5–7 years [5].

Its prevalence is closely related to social and economic conditions. Because of the sharp decline in postinfectious GN, the disease has been forgotten in industrialized countries; however, there is evidence of outbreaks in various parts of the world [6]. In rich countries, it is more common in the elderly, especially in association with debilitating conditions such as alcoholism,

A. Q. B. da Silva (✉)
Universidade Federal do Rio Grande do Norte, Natal, Brazil
e-mail: dmi@ccs.ufrn.br

G. M. Kirsztajn
Universidade Federal de São Paulo, São Paulo, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_26

neoplasia, diabetes, and intravenous drug use [7]. In the Italian Biopsy Registry [8], GNDA is now more common after the age of 60 (0.9 patients per million) than before that age (0.4 patients per million). And in children under 15, the incidence went from 2.6 to 3.7% in the period from 1987 to 1992 to just nine cases from 1992 to 1994. The incidence of GNDA in children and adults around the world has been falling in recent decades [9, 10]. This trend is probably due to improved living conditions, the early and effective use of antibiotics, and the growing practice of water fluoridation, which attenuates the expression of *Streptococcus pyogenes* virulence [11, 12] (Table 26.1).

In the past, the etiology of postinfectious GN was almost exclusively related to streptococcal infection, however, nowadays, there is a much broader spectrum of possible causative agents defined, including staphylococci, gram-negative bacteria, intracellular bacteria (Chlamydia, Mycoplasma), viruses (herpes simplex, cytomegalovirus, Epstein–Barr virus, hepatitis B, influenza), fungi (Candida, Histoplasma), and parasites (Toxoplasma, Plasmodium malariae) [12] (Table 26.2).

Similarly, outbreaks of the disease coincide with economic decline, poor hygiene, and insufficient medical care. These epidemics, although fewer in number, have also been observed in Japan, Western Europe, and North America [13–15]. In Brazil, a major outbreak of NAFLD occurred in 1998, associated with unpasteurized milk, when 253 cases of acute NAFLD were reported in the state of Minas Gerais [16].

It is not always possible to identify the pathogenic strains, but it is usually the nephritogenic group A β-hemolytic streptococcus that is responsible, especially when there is transient hypo-

Table 26.1 Post-streptococcal GN epidemics with more than 100 cases

Year	Location	Number of cases	Affected population	Infection site	Type of streptococcus
1951–1953	Bainbridge	180	Military recruits	Oropharynx	M12
1964–1965	San Fernando, Trinidad, Índias Ocidentais	760	Rural and urban	Skin	M55, M49
1968	Maracaibo, Venezuela	384	Rural	Oropharynx	Not determined
1967–1968	San Fernando, Trinidad, Índias Ocidentais	540	Rural and urban	Skin	M49, M60
1974	Maracaibo, Venezuela	200	Urban	Skin	Not determined
1974	Baracoa, Guantanamo, Cuba18	295	Rural and urban	Skin and oropharynx	Not determined
1986	San Fernando, Trinidad, Índias Ocidentais	181	Urbano	Skin	M73, M48, M55, M57, 59
1995	Yerevan, Armênia	196	Rural and urban	Oropharynx	Not determined
1995	São José, Costa Rica	103	Rural and urban	Skin and oropharynx	Not determined
1995	Vilnius, Lituânia	8,3/100.000 crianças	Rural and urban	Skin and oropharynx	Not determined
1998	Nova Serrana (MG) - Brasil	135	Rural	Unpasteurized milk	*Streptococcus zooepidemicus*
1998–2001	Lima, Peru	186	Urban	Oropharynx	Not determined

Source: Rodriguez-Iturbe B (2008) [7]

Table 26.2 Prevalence of infectious agents that can cause postinfectious GN

Agents	Children and young adults	Elderly (> 65 years)
Group A beta-hemolytic streptococci type 12, M 1-4, 18, 25, 31, 49, 52, 55-57, 59-61, group C, group G	95%	16–30%
Staphylococcus epidermidis, S. haemolyticus, S. aureus	Uncommon	24–60%
Escherichia coli	Very rare	5–10%
Pseudomonas, Acinetobacter, Serratia, Proteus, Klebisiella, Enterobacter	Very rare	2–3%
Mycobacteria (may be associated with chronic GN), Neisseria (associated with membranoproliferative GN)		Rare (<1%)

Source: Stratta, 2014 [12]
GN glomerulonephritis

complementemia and a parallel increase in the number of children with scarlet fever and skin infections. It is necessary to be aware of the possibility of *S. zooepidemicus* as the etiological agent of epidemic GNPE, transmitted to humans by unpasteurized dairy products, affecting mainly adults, and which after the acute phase, was characterized by severe clinical manifestations in the epidemic that occurred in Brazil [16].

26.3 Pathophysiology

26.3.1 Hypothesis of GN Pathogenesis by Immune Complexes

Group A streptococci were recognized as the only strain capable of causing GN. Group C streptococci, however, have caused recent epidemics of NAFLD, specifically *S. zooepidemicus*, and therefore nephritogenic antigens are present and possibly shared by streptococci from several groups [17].

Two antigens are currently being actively investigated as potential causes of GNPE: nephritis-associated plasmin receptor (NAPlr) [18, 19] and a cationic cysteine known as streptococcal pyrogenicexotoxin B (SPEB) [20–22]. These two enzymes are capable of activating the alternative pathway of the complement system [17].

NAPlr deposits are present in early biopsies of patients in the acute phase of GNDA and levels of anti-NAPlr antibodies are detected in the serum of 92% of patients with GNPE and in 60% of complicated streptococcal infections in Japan [18]. Recent publications (2007) by Fujino et al. [23] have shown that the gene sequence and in vitro expression of NAPlr is not restricted to strains isolated from patients with GNPE, but is also present in group A, C, and G streptococci.

Both SPEB7 and NAPlr72 are capable of chemotactic induction of IL-6, IL-8, and TNF to mesangial cells, promoting increased expression of adhesion molecules when they react with leukocytes. These findings highlight the potential inflammation caused by these nephritogenic antigens [24].

26.3.2 Hypothesis of GN Due to IgA Deposition

Postinfectious GN with IgA deposition is not completely understood and may differ from "classical" ADGN (Table 26.3). Some factors related to bacterial characteristics seem to be crucial, especially with methicillin-resistant *S. aureus* (MRSA), in which nephritis may be induced by a superantigen (toxic shock syndrome toxic exotoxin—TSST-1), which stimulates high cytokine activity, IgA production, and immune complex deposition. However, also host-related factors have been investigated to explain the predominant IgA deposition: diabetic patients are frequently affected by subclinical infections and also have a reduced IgA clearance, which may be responsible for its deposition in the glomerulus [12] (Table 26.3).

Table 26.3 Main mechanisms involved in the pathogenesis of acute postinfectious glomerulonephritis

	Mechanism of kidney injury	
Hypothesis	PSGN	Acute post-staphylococcal GN with IgA deposits
Circulating IC	Glomerular deposition of IC (Ig and bacterial antigens) and activation of the alternative complement pathway	Exotoxin superantigens stimulate the production of an IgA, forming IgA IC
Formation of IC "in situ"	IC formation "in situ," due to deposition of streptococcal antigens	It may be a result of overproduction of IgA
Cellular infiltrate	Granulocytes, monocytes, and lymphocytes, attracted by complement activation (classical or alternative pathway)	The exotoxin superantigen TSST-1 stimulates abnormal cytokine production, recruiting inflammatory cells
Autoimmune reactions	Molecular mimicry with glomerular proteins (laminin, vimentin, collagen)	Cryoglobulinemia formation and RF formation due to a dysregulated immune response to bacterial antigens and superantigens
Nephritogenic bacterial antigens	NAPlr/SPEB, capable of binding to activated plasmin	Possible role of staphylokinase, which is capable of activating plasmin and may play a glomerular inflammatory role
Host predisposition	HLA II (DRB1 and DPA1-DPB1)	Reduced IgA clearance and favored IgA deposition, such as aberrant glycosylation and underlying diabetic nephropathy

Source: Stratta, 2014 [12]
IC immune complexes, *Ig* immunoglobulins, *BM* basement membrane, *RF* rheumatoid factor, *GN* glomerulonephritis, *PSGN* post-streptococcal glomerulonephritis, *TSST* toxic shock syndrome toxin

26.4 Histopathology

Patients who are asymptomatic or who report mild symptoms may have a biopsy showing mild glomerular involvement, while patients with diffuse proliferative GN are more likely to have a very symptomatic acute diffuse nephritic syndrome (with hematuria, proteinuria, edema, hypertension, and acute kidney injury). The formation of epithelial crescents is not common in post-streptococcal GN and, when present in more than 30% of glomeruli, is associated with a poor prognosis. Rapidly progressive GN is not common, occurring in less than 5% of cases [2].

In a longitudinal study carried out in Mexico [15], clinical-pathological data from 450 children between the ages of 1.5 and 16 with acute postinfectious GN are presented, with a follow-up of 12 years. Renal biopsies were obtained from 127 patients, 79.5% of whom had endocapillary proliferative GN and the rest had proliferative GN with or without crescents and even membranoproliferative GN.

26.4.1 Optical Microscopy

The most common histological finding in GNPE is proliferative glomerulonephritis with diffuse hypercellularity. In the early stages, cellular infiltration is exudative and characterized by the endocapillary presence of neutrophils, endothelial cells, monocytes, and lymphocytes, with a reduction in capillary lumens and urinary space. In severe cases, extracapillary proliferation may be present, but it usually has a focal distribution and does not affect more than 50% of glomeruli. On Masson's stain, the typical subepithelial fuchsinophilic (red) "humps" can be seen [5].

In a later phase of the disease (around 2 weeks after onset), glomerular hypercellularity is progressively reduced and histology is characterized by mesangial expansion of varying degrees and complete recovery of glomerular damage. This phase can last a few weeks. If glomerular infiltration persists for more than 6 months after the onset of the disease, the possibility of NG related to another infection should be considered [5, 13].

26.4.2 Immunofluorescence

Immunofluorescence findings follow the same chronological pattern observed in light microscopy. The C3 deposit is always present in a granular pattern and IgG deposits are the most commonly observed in early biopsies, while IgM, IgA, and the C1q complement fraction are rarely seen. Three different immunofluorescence patterns have been identified. The "starry sky" pattern is characterized by subepithelial granular deposits with scattered distribution in the tuft: it is typical of the early stages of the disease and is usually associated with diffuse endocapillary proliferation. The "garland" pattern is also found in around 25% of biopsies taken in the early stages of the disease: it is characterized by large granular deposits in the basement membrane, which often merge and can more often be associated with subendothelial and mesangial deposits. This immunofluorescence pattern is generally related to more severe clinical manifestations and prognosis. In the later stages of the disease, corresponding to mesangial proliferation, the deposits are composed almost exclusively of C3 and are located in the mesangium, defining a "mesangial pattern" [5, 13].

26.4.3 Electron Microscopy

In the early stages of the disease, the capillary lumens are closed by the cellular infiltrate and humps can commonly be seen on the capillary walls. These deposits are located on the epithelial side of the basement membrane over the lamina densa. There may be just a few deposits scattered in the tuft or numerous deposits close together, corresponding to the "starry sky" and garland immunofluorescence patterns, respectively. In the later stages of the disease, when the subepithelial deposits are reduced, new deposits appear in the mesangium [5, 12, 13].

26.4.4 Diagnosis

The diagnosis of GNPE is based on the clinical findings of acute nephritis, which include macro- or microscopic hematuria ("cola-colored urine"), the presence of erythrocyte dysmorphism with or without hematic cylinders, varying degrees of proteinuria, edema, and hypertension, as well as the demonstration of recent infection by group A beta-hemolytic streptococcus. This recent infection is documented by positive oropharyngeal or skin cultures or serological tests [2]. C3 levels are almost always reduced, due to activation of the alternative complement pathway, a situation that resolves within 6–8 weeks. If C3 levels remain low after this period, other diseases should be taken into consideration (C3 glomerulopathy, membranoproliferative GN, subacute endocarditis). In addition, most patients present with transient hypergammaglobulinemia [12].

During the latency phase, isolated urinary abnormalities can be found and, after this period, nephritis can present subclinically or with a nephritic syndrome, the former being five times more frequent during epidemics [25].

In adults, the clinical presentation of GNPE is the same as in children, but the site of infection can also be the lower airways, lungs, urinary tract, and subclinical infections. Often (in 30% of cases), a GNPE is diagnosed in immunocompromised patients, including AIDS patients and intravenous drug addicts. In this situation, the disease can be more aggressive than in the pediatric population: 25% of adult patients may need dialysis and complete recovery is seen in only 40–50% of patients [26].

In the elderly, GNPE can have different characteristics, as this situation is more common in immunocompromised patients and those with multiple comorbidities (neoplasia, alcoholism, diabetes). Primary infections are often localized to the skin, including surgical wound infections and bloodstream infections. The latency between

infection and nephritis is, in most cases, absent, so that infection is diagnosed at the same time as nephritis in almost 50% of cases, since an infectious disease in these patients may not be recognized for a prolonged period, due to the absence of classic signs and symptoms of an infection in 20-30% of patients. The clinical picture is usually complicated by underlying comorbidities, such as decompensated heart failure, due to water and salt retention. Complete recovery is uncommon and residual chronic kidney disease is observed in around 60% of patients. Death can be a relatively common outcome of GNPE in these patients (20–25%). The main prognostic factors include the presence of diabetic glomerulosclerosis, tubular atrophy, interstitial fibrosis, and the number of crescents, as well as the patient's age, elevated baseline serum creatinine at presentation, the need for renal replacement therapy, and the degree of residual proteinuria after resolution of the acute disease [12].

Kidney biopsy is rarely necessary, especially in children, while in adult or elderly patients a biopsy is justified if there is an atypical presentation or evolution, such as progressive renal failure, absent or delayed recovery of function, persistence of low C3 levels, nephrotic range proteinuria, and persistence of proteinuria [12], which may require immediate immunosuppressive therapy [26].

26.5 Post-covid

Coronavirus disease 2019 (COVID-19) was announced at the end of 2019 by the WHO as a global pandemic, and clinical symptoms ranged from asymptomatic to severe respiratory distress syndrome. In 2020, many COVID-19 vaccines were announced and approved internationally on an emergency basis, with subsequent questions about their reactogenicity, especially in relation to polyclonal expansion of B cells, formation of immune and vascular complexes [27], which can cause various disorders, although rare, mainly thrombotic events, myelitis, vasculitis, and myocarditis. The administration of some messenger ribonucleic acid (RNA) vaccines was eventually associated with the appearance of glomerulopathies [28].

A temporal relationship between de novo and relapsing GN after COVID-19 vaccination has been reported in minimal lesion disease (ML), IgA nephropathy (IgAN), membranous nephropathy (MN), lupus nephritis (LN), anti-basalglomerular membrane antibody disease, and ANCA-associated pauci-immune GN (ANCA-GN) have been documented [29].

26.5.1 Prognosis

The prognosis and outcome of GNDA depend on age, gender, comorbidities, the degree of renal failure reflected by clinical and histological characteristics, the site of infection, and the microorganism involved. School-age children recover completely in over 95% of cases. Children have the best prognosis, followed by healthy adults. Adults with risk factors for kidney damage are more likely to develop chronic kidney damage after postinfectious GN [30].

Patients who develop postinfectious GN in the setting of an epidemic generally have an excellent prognosis, particularly children and healthy adults [31]. In contrast, GNDA associated with sporadic infections in adults tends to have a worse prognosis, with up to 60% of adults developing chronic kidney disease [9, 32]. This may be due to the more severe nature of symptomatic sporadic cases, which otherwise do not come to clinical attention. Streptococcal infections are associated with a better outcome compared to other infectious organisms [9] Table 26.4.

26.5.2 Treatment

There is no specific treatment for GNDA. Treatment is basically supportive, aimed at treating the clinical manifestations, such as controlling arterial hypertension, using loop diuretics (most commonly furosemide) at a dose according to the edema, diuresis and degree of renal insufficiency, sodium and fluid restriction,

Table 26.4 Long-term prognosis of GNPE: summary of series published after the year 2000

Location	Patients under follow-up (N)	Follow-up (anos)	Albuminuria (%)	Hematuria (%)	Hypertension (%)	Renal dysfunction
Maracaibo, Venezuela	110	15–18	7,2	5,4	13,7	Increased sCr in 0.9% of patients
Australian North, territory	63	>13	13	21		
Minas Gerais, Brazil	56	5	8		30	8% (Crcl≤ 60ml/min)

Source: Rodriguez-Iturbe B (2008) [7]
CrCl creatinine *clearance*, *sCr* serum creatinine

or calcium channel blockers, vasodilators, angiotensin aldosterone system blockers and angiotensin receptor blockers, bearing in mind the risk of hyperkalemia with these last two medications. Some patients may need dialysis, although this is rare in GNPE. This acute phase lasts around 2 weeks [2, 12].

Immunosuppressive drugs are not indicated in most cases of postinfectious GN in children, but they can be used in cases of progressive renal failure and/or biopsy showing the formation of glomerular crescents in 30–50% of the glomeruli, which is a strongly negative prognostic factor [33]. In these cases, the preferred therapy is generally based on intravenous pulse therapy with methylprednisolone 500–1000 mg/day or 10–15 mg/kg/day for 3 consecutive days, followed by oral corticosteroid therapy, according to clinical progression and recovery of renal function. If the biopsy shows severe interstitial infiltrate, which can be a poor prognostic factor, a short period of oral steroids can be useful [34]. There are no controlled studies investigating these therapies in adults or the elderly with GNDA associated with progressive renal failure, but uncontrolled studies and case reports suggest a success rate with corticosteroid pulses in around 60% of patients treated [12].

26.5.3 Role of Antibiotics in the Treatment of PSGN

The Infectious Diseases Society of America [35] (IDSA) and textbooks that discuss the subject, including Principles and Practice of Infectious Diseases [36] by Bennet et al., state that treating group A strep pharyngitis with antibiotics does not interfere with the development of PSGN.

It is important to note that the authors of the Principles and Practice of Infectious Diseases [36] recommend treating those who develop PSGN with penicillin in order to eradicate the nephritogenic streptococcal strain, and the IDSA guidelines stipulate the eradication of nephritogenic strains in community outbreaks of acute PSGN.

26.6 Conclusion

The epidemiology of NAFLD is changing in Western countries, along with the progressive aging of the population. Post-streptococcal GN should always be considered in the differential diagnosis of elderly patients with renal failure associated with active urinary sediment. A good knowledge of its atypical presentations and evolution in the elderly patient is crucial for a correct diagnosis and prompt treatment.

Renal biopsy is rarely necessary, especially in classic forms in children, where GNDA can be diagnosed through the finding of an acute nephritic syndrome with low C3 levels. In adults or the elderly, biopsy is most often performed to confirm the diagnosis in the event of an atypical presentation or evolution (persistent or rapidly progressive renal failure, absent or delayed functional recovery, persistent low C3, nephrotic proteinuria, or persistent significant proteinuria).

The differential diagnosis must be made with IgA glomerulopathy, in which the infection is concomitant with the onset of nephritis, there is a picture of macroscopic hematuria, which is usually redicivocal and renal failure at presentation is rare, and with membranoproliferative GN, which has persistent low C3 levels and does not recover without specific therapy. This differentiation is important because the therapeutic approach is different. In general, post-streptococcal GN has a benign evolution, with full recovery in 2–4 weeks and without leaving sequelae in renal function.

26.7 Take Home Message

- For health professionals working in endemic areas with limited resources, the prevention and control of post-streptococcal glomerulonephritis (PSG) is crucial.
- It is essential to implement effective prevention strategies, such as promoting good personal and community hygiene practices, and ensuring access to early and appropriate medical care for streptococcal infections.
- Educating the community about the signs and symptoms of streptococcal pharyngeal and skin infections can help with early detection and timely treatment, preventing kidney complications. In addition, continuous training of health professionals in the diagnosis and management of GNPEs can improve patient outcomes.
- These measures are in line with several of the World Health Organization's Sustainable Development Goals (SDGs), particularly SDG 3 (Health and Well-being), which aims to combat communicable diseases and ensure universal access to health services. Also relevant is SDG 6 (Drinking Water and Sanitation), by improving access to clean water and adequate sanitation to reduce the incidence of infections. Education for sustainable development, promoted by SDG 4 (Quality Education), can help teach hygiene practices in schools. Reducing inequalities under SDG 10 is essential, as vulnerable populations are the most affected by GNPE. And finally, SDG 1 (Eradication of Poverty) highlights the need for equal access to basic resources and services, including health.
- Integrating these efforts in the context of the SDGs can not only help control and prevent GNPE, but also promote sustainable and healthy development for affected communities

References

1. Kupin W. Viral-associated GN: hepatitis B and other viral infections. Clin J Am Soc Nephro. 2017;12:1529–33.
2. Requião-Moura LR, et al. Tratado de Nefrologia, 1°Ed. São Paulo: Atheneu; 2017. p. 323–32.
3. Bright R. Tabular view of the morbid appearances in 100 cases connected with albuminous urine. Guy's Hosp Rep. 1836:380–48.
4. Rodriguez-Iturbe B, Rubio L, Garcia R. Attack rate of poststreptococcal nephritis in families. Lancet. 1981;317:401–3.
5. Nast C. Infection-related glomerulonephritis: changing demographics and outcomes. Adv Chronic Kidney Dis. 2012;19:68–75.
6. Sarkissian A, Papazian M, Azatian G, et al. An epidemic of acute postinfectious glomerulonephritis in Armenia. Archives of Disease in Childhood. 1997;77:342–4.
7. Rodriguez-Iturbe B, Musser JM. The current state of poststreptococcal glomerulonephritis. J Am Soc Nephrol. 2008;19:1855–64.
8. Gesualdo L, Di Palma AM, Strippoli MLF, et al. The Italian experience of the national registry of renal biopsies. Kidney Int. 2004;66:890–4.
9. Kanjanabuch T, Kittikowit W, Eiam-Ong S. An update on acute postinfectious glomerulonephritis worldwide. Nat Rev Nephrol. 2009;5:259–69.
10. Ilyas M, Tolaymat A. Changing epidemiology of acute post-streptococcal in Northeast Florida: a comparative study. Pediatr Nephrol. 2008;23:1101–6.
11. Thongboonkerd V, Luengpailin J, Cao J, et al. Fluoride exposure attenuates expression of Streptococcus pyogenes virulence factors. J Biol Chem. 2002;277:16599–605.
12. Stratta P, Musetti C, Barreca A, et al. New trends of an old disease: the acute post infectious glomerulonephritis at the beginning of the new millenium. J Nephrol. 2014;27:229–39.
13. Poon-King T, Mohammed I, Cox R, et al. Recurrent epidemic nephritis in South Trinidad. N Engl J Med. 1967;277:728–33.

14. Reinstein CR. Epidemic nephritis at Red Lake. Minnesota. Pediatr. 1955;47:25–34.
15. Rodriguez-Iturbe B, Garsia R, Rubio L, et al. Epidemic glomerulonephritis in Maracaibo. Evidence for progression to chronicity. Clin Nephrol. 1976;5:197–206.
16. Pinto SWL, Mastroianni-Kirsztajn G, Sesso R. Ten-year follow-up of patients with epidemic post infectious glomerulonephritis. PLoSOne. 2015;10:e0125313.
17. Rodriguez-Iturbe B, Batsford S. Pathogenesis of poststreptococcal glomerulonephritis: a century after Clemens von Pirquet. Kidney Int. *2007*;71:1094–104.
18. Yoshizawa N, Yamakami K, Fujino M, et al. Nephritis-associated plasmin receptor and acute poststreptococcal glomerulonephritis: characterization of theantigen and associated immune response. J Am Soc Nephrol. 2004;15:1785–93.
19. Oda T, Yamakami K, Omasu F, et al. Glomerularplasmin-like activity in relation to nephritis-associated plasmin receptor inacute post-streptococcal glomerulonephritis. J Am Soc Nephrol. 2005;2005(16):247–54.
20. Poon-King R, Bannan J, Viteri A, et al. Identification of an extracellular plasmin binding protein from nephritogenic streptococci. J Exp Med. *1993*;178:759–63.
21. Parra G, Rodríguez-Iturbe B, Batsford S, et al. Antibody to streptococcal zymogen in the serum of patients with acute glomerulonephritis: A multicentric study. Kidney Int. *1998*;54:509–17.
22. Cu GA, Mezzano S, Bannan JD, et al. Immunohistochemical and serological evidence for the role of streptococcal proteinase in acute post-streptococcal glomerulonephritis. Kidney Int. *1998*;54:819–26.
23. Fujino M, Yamakami K, Oda T, et al. Sequence and expression. of NAPlr is conserved among group A streptococcal isolated from patients with acute post-streptococcal glomerulonephritis (APSGN) and non-APSGN. J Nephrol. *2007*;20:364–9.
24. Khan F, Yamakami K, Mahmood J, et al. Alterations of cell adhesion molecules in human glomerular endothelial cells in response to nephritis-associated plasminogen receptor. Exp Nephrol. 2007;105:53–64.
25. Barros RT, Ribeiro-Alves MAVF, Mastroianni-Kirsztajn G, et al. Glomerulopatias: patogenia, clínica e tratamento, 3° edição. São Paulo. 2012:449–69.
26. Nasr SH, Radhakrishnan J, D´Agati VD. Bacterial infection-related glomerulonephritis in adults. Kidney Int. 2013;83:792–803.
27. Eison TM, Ault BH, Jones DP, et al. Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatr Nephrol. *2011*;26(*2*):165–80.
28. Berrios X, Lagomarsino E, Solar E, et al. Post-streptococcal acute glomerulonephritis in Chile-20 years of experience. Pediatr Nephrol 2004. 2004;19(3):306–12.
29. Lien JW, Mathew TH, Meadows R. Acute post-streptococcal glomerulonephritis in adults: a long-term study. Q J Med. 2010;48(189):99–111.
30. Shank JC, Powell TA. A five-year experience with throat cultures. J Fam Pract. 1984;18:857–63.
31. McIsaac WJ, White D, Tannenbaum D, et al. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ. *1998*;158:75–83.
32. Edmonson MB, Farwell KR. Relationship between the clinical likelihood of group A streptococcal pharyngitis and the sensitivity of a rapid antigen-detection test in a pediatric practice. Pediatrics. *2005*;115:280–5.
33. El-Husseini AA, Sheashaa HA. Sabry AA et al Acute post infectious crescentic glomerulonephritis: clinicopathologic presentation and risk factors. Int Urol Nephrol. 2005;37:603–9.
34. Hoy WE, White AV, Dowling A, et al. Post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease in later life. Kidney Int. 2012;81(10):1026–32.
35. Musser JM, DeLeo FR. Toward a genomewide systems biology analysis of host-pathogen interactions in group A *Streptococcus*. Am J Pathol. *2005*;2005(167):1461–72.
36. Beres SB, Musser JM. Contribution of exogenous genetic elements to the metagenome of group A *Streptococcus*. PLoS One. *2007*;2:e5.

27 Staphylococcal Infections and Kidney Disease

Maria Almerinda Vieira Fernandes Ribeiro Alves

27.1 Introduction

Staphylococcus is a genus of spherical, gram-positive bacteria (*when in contact with gentian violet dye, it becomes violet or dark blue in color*) and is one of the most common pathogens in humans. Of the 33 known species, 17 have been isolated in human samples. Of the coagulase-negative species, those that when in contact with plasma do not form clots are considered to be of pathogenic importance to humans, mainly *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*. The coagulase-positive *Staphylococcus aureus* species is considered the most pathogenic one for humans, and it is responsible for the persistent colonization of approximately 10–20% of the population (particularly the skin and nasal passages), making these individuals potential vectors for community or hospital contamination. In healthy individuals and normal situations, the colonization does not seem to be a problem [1].

S. aureus is related to the onset of diseases that range from simple infections (cellulitis, folliculitis, impetigo) to severe infections (pneumonia, meningitis, endocarditis, septic shock, septicemia, osteomyelitis, septic arthritis, and others), and it is considered the second most common pathogen involved in bloodstream infections (bacteremia) [2, 3]. The progression of these infections to sepsis and multiple-organ dysfunction is responsible for several intensive care unit admissions. The overall mortality associated with staphylococcus bacteremia is around 15–20% and, in cases requiring intensive care, 35–50% [4].

S. aureus infections may be due to methicillin-resistant (MRSA) or methicillin-susceptible (and MSSA) bacteria. The ratio of resistant and susceptible bacteria to methicillin (oxacillin) varies according to the studied groups. The dynamic evolution of antibiotic resistance of this staphylococcus is the characteristic responsible for maintaining the importance of this agent as a pathogen in human infectious processes. Methicillin-resistant strains (the first semisynthetic penicillin for clinical use) are common in hospital settings, thus making treatment limited to the glycopeptides (particularly vancomycin and teicoplanin). MRSA-associated bacteremia show higher mortality, morbidity, and costs than methicillin-susceptible staphylococci [5]. Vancomycin-resistant strains started to be described at the end of the twentieth century, showing the adaptability of the microorganism [6].

MRSA infection is considered one of the leading causes of nosocomial infections and a major cause of morbidity and mortality. Methicillin-resistant staphylococcus can be classified into

M. A. V. F. R. Alves (✉)
Universidade de Campinas, Campinas, SP, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_27

hospital associated (HA-MRSA) or community associated (CA-MRSA) [7].

Respiratory, soft tissue, joint, and bone infections are among the most common diagnoses of severe infections by this agent. Among the cases of bloodstream infection (hospital or community), *Staphylococcus aureus* is one of the most commonly found bacterial agents.

Important risk factors for severe infections are heart disease, diabetes mellitus, obstructive pulmonary disease, and neoplasms, but the highest risk involves patients on hemodialysis, peritoneal dialysis, HIV patients, and transplant patients [3].

The association between the nephrologist's daily routine and *Staphylococcus* occurs in several ways that include practically all activities related to the specialty (chronic renal replacement therapy, acute kidney injury, interventional nephrology, and clinical nephrology).

27.2 Staphylococcus and Chronic Kidney Disease

27.2.1 Hemodialysis

Of the total of *S. aureus*-associated bacteremia, 15–66% occur in individuals with dialytic chronic kidney disease, and, in dialysis patients, this pathogen accounts for approximately 40% of severe infections [8]. There are reports of up to 100-fold higher incidence of severe MRSA infection in chronic dialysis patients than that observed in the general population [9].

Among the infectious conditions, in patients on chronic renal replacement therapy (transplantation, hemodialysis (HD), or peritoneal dialysis), the risk of blood-stream infection is approximately 30-fold higher when compared to the control group, with the group on hemodialysis being the most susceptible (about 90% of cases) [10]. The occurrence of *S. aureus* blood infection in patients on chronic hemodialysis is particularly associated with vascular access infection, especially when using central venous catheters, when compared to arteriovenous fistulas or vascular grafts [10, 11]. Duration of catheterization, number of dialysis sessions, and length of hospitalization constitute a risk of colonization and sepsis. Bacteremia occurs more often in catheters that remain for more than 10 days [12]. Infections associated to vascular access may originate from extraluminal (earlier onset) or intraluminal (later onset) colonization.

Patients on chronic hemodialysis are colonized by MRSA in approximately 3–20% of cases, reaching 65% in some studies [13]. These individuals (colonized by MRSA) are about 11 times more likely to develop pathogen infections. Compared to colonization and subsequent infection by methicillin-susceptible staphylococcus (MSSA), MRSA patient mortality is five times higher [14].

In patients on chronic hemodialysis, it is possible to observe in some studies, an increase in the number of colonized patients from 5% to 16% after 6 months. This event is associated with the presence of diabetes and exposure to previous antibiotic therapy [15]. This observation reinforces the importance of the implementation and maintenance of preventive measures to minimize contamination in these individuals, remembering that infection development generally has colonization as a prerequisite [16].

Infections resulting from bacteremia associated with vascular access in hemodialysis patients are endocarditis, osteomyelitis, septic arthritis, and sepsis.

27.2.2 Peritoneal Dialysis

Peritonitis remains, among individuals undergoing peritoneal dialysis, an important cause of catheter removal, transfer to hemodialysis, skin infection (around the catheter), hospitalization, and death. *Staphylococcus epidermidis* and *Staphylococcus aureus* are the two infectious agents most often associated with this peritonitis. There is no evidence to indicate whether oral or local therapy to try to decolonize patients with the pathogen has any difference in the outcome in relation to peritonitis [17].

Some antimicrobials (particularly mupirocin) applied locally (nostrils and around the catheter) have been used to try to minimize colonization,

since the association between carriers and staphylococcus infections has been demonstrated [18]. A recent meta-analysis showed a lower risk of infection (compared to the control group) by *S. aureus* at the catheter exit site in peritoneal dialysis in patients submitted to local prophylaxis with antibiotic therapy, but it was not possible to observe this difference in relation to the onset of peritonitis [17].

27.3 Staphylococcus and Acute Kidney Injury

27.3.1 Sepsis

Sepsis is the main cause of association with acute kidney injury (AKI) in hospitals and intensive care units. Approximately 50% of AKI patients in the intensive care setting have sepsis [19].

Acute kidney injury (defined by the RIFLE/AKIN criterion) (Table 27.1) associated with sepsis (Table 27.2) (defined by the Systemic Inflammatory Response Syndrome (SIRS) criterion), called by some authors as septic acute kidney injury, affects 10–60% of the patients with sepsis and has higher mortality, regardless of whether the patient is in an intensive care setting or not, compared to patients with sepsis without kidney injury or acute kidney injury without sepsis [20].

Although gram-negative bacteria are, in most studies, the most commonly observed pathogens in sepsis, *S. aureus* is the most common gram-positive bacterial agent in septic acute kidney disease. MRSA is identified in about 10% of gram-positive cases and is the infectious agent associated with higher mortality in these patients [21].

Chronic dialysis patients have a 40-fold higher risk than the general population to develop severe sepsis, as well as a higher risk of death [22].

Studies show that around 40% of sepsis survivors older than 65 years are hospitalized again, after discharge, within a period of approximately 90 days. A new sepsis episode is the main cause of this readmission, with renal failure being the fourth most common cause. Both situations show a higher diagnostic incidence in relation to the first admission controls [23].

Table 27.1 Definition of acute kidney injury

Definition
Serum creatinine increase ≥0.3 mg/dL in 48 h Or
Serum creatinine increase 1.5-fold from baseline (last 7 days) Or
Decreased urine volume < 0.5 mL/kg /hour in 6 h

Adapted from Parmar et al. [20]

Table 27.2 Definition of sepsis pictures according to SIRS (systemic inflammatory response syndrome)

SIRS (defined by the presence of ≥2 of the criteria in the next column)	Temperature > 38 °C or < 36 °C Heart rate > 90 bpm Respiratory rate > 20 rpm or $PaCO_2$ > 30 mmHg Leukocytes >12.000/mm^3, <4.000/mm^3 or >10% immature forms
Sepsis	Confirmed or suspected infection associated with ≥ SIRS criteria
Severe sepsis	Sepsis associated with one or more organ dysfunction
Septic shock	Presence of severe sepsis associated with unresponsive volume hypotension
Septic acute kidney injury	Acute kidney injury defined by RIFLE/AKIN criteria associated with sepsis

Adapted from Parmar et al. [20]

The pathophysiological mechanisms involved in kidney injury in sepsis are several and not yet fully understood [19]. Interestingly, mitochondrial response involvement in kidney inflammation and oxidative cell damage was demonstrated in mouse proximal renal tubules, in sepsis associated with *S. aureus*, suggesting the possibility that pathogen-specific characteristics may contribute to this pathophysiology [24].

The manipulation and maintenance of vascular accesses for renal replacement therapy are risk factors for the development of staphylococcus-related infections. When discussing the early or late indication of RRT in acute kidney injury, one argument in favor of the cost-benefit analysis of the procedure is the fact that, even without a difference in mortality, there is less bacteremia in individuals with late indication [25].

It should be noted that, regardless of the cause, the diagnosis of acute kidney injury is associated with a higher future risk of chronic kidney disease, making this characteristic a warning sign for renal follow-up in these patients [26].

27.3.2 Vancomycin

Vancomycin is a glycopeptide antibiotic used for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). It is worth remembering that after the identification of methicillin-resistant Staphylococcus and, in 1953, the development of vancomycin, the FDA approved its use in less than 5 years. This rapid approval was characterized by the disease severity caused by the bacterium. With the increased resistance of this bacterium, vancomycin is currently the most often prescribed antibiotic for these cases. To attribute nephrotoxicity to vancomycin has been a point of disagreement, given that the use of this drug alone is uncommon and, in general, other potentially nephrotoxic drugs are associated. However, there are compelling reports about this drug characteristic [26]. The following are considered risk factors for this nephrotoxicity: preexisting kidney failure (the drug is excreted by the kidneys); residual serum levels (before the next dose); dose, duration, and type of administration (continuous and intermittent), and although very controversial, the continuous administration is suggested to decrease the chance of renal toxicity; obesity (dose calculation depends on weight); association with hypovolemia; and other nephrotoxic drugs [27, 28].

27.3.3 Staphylococcus and Immune-Mediated Diseases

Another aspect related to staphylococcal involvement in kidney disease in humans is related to immunologically mediated diseases. The triggering mechanisms may be due to autoimmunity (due to loss of tolerance) or molecular mimicry, due to the action of the immune system (innate or acquired) in the relationship with the pathogen [29].

27.3.4 Staphylococcus-Associated Glomerulonephritis

Described in 1995 [30] in a methicillin-resistant strain, a predominance of *Staphylococcus* has been observed in elderly adults (46%) in postinfectious glomerulonephritis, with a predominance of *S. aureus* [31].

The preference for designating this glomerular disease as staphylococcal-associated glomerulonephritis [32] is due to different postinfectious characteristics and the presence of active infection. Clinical and laboratory findings are the common ones to this type of disease (hypertension, edema, proteinuria, hematuria, leukocyturia), but with a large number of patients with significant acute loss in glomerular filtration rate and C3 and C4 hypocomplementemia. The infectious processes are located mainly in the skin (cellulitis, ulcers, surgical infections, abscesses) and in the viscera (pneumonia, endocarditis, osteomyelitis). Thus, it is possible to include, with the term staphylococcal-associated glomerulopathy, the glomerulonephritis described in association with bacterial endocarditis, osteomyelitis, and shunts.

Renal biopsy is characterized by diffuse endocapillary proliferation (as observed in other pathogens). Interestingly, in immunofluorescence, there is a predominance of IgA and C3 codeposition, unlike that observed in other postinfectious forms (predominantly IgG and C3). The deposits observed by electron microscopy are subendothelial, mesangial, and subepithelial. Thus, this glomerulopathy has presentation characteristics that differentiate it from postinfectious glomerulonephritis.

27.4 Granulomatosis with Polyangiitis (Wegener's Granulomatosis)

Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis, WG) is an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, generally showing a cytoplasmic pattern (proteinase 3 is the related antigen) with a mortality rate in the last decade, in the first year of diagnosis, of 10%, and with periods of exacerbation that affect the long-term prognosis. Renal impairment is common (80%), usually with rapid progress (characterized by hematuria and acute kidney injury). The treatment requires long-term immunosuppressants and attention to possible recurrence.

In individuals diagnosed with granulomatosis with polyangiitis (GPA), nasal colonization by *Staphylococcus aureus* was identified as an independent risk factor for relapse [33]. In more than 70% of GPA patients with the pathogen, at least one superantigen was identified (antigens capable of polyclonal activation of up to 25% of T cells) [34].

In current guidelines proposed for the treatment of GPA, the use of trimethoprim-sulfamethoxazole is suggested as an adjunct therapy to the maintenance treatment of these patients (especially in cases of upper respiratory involvement) [35]. This suggestion is based on a 60% reduction in GPA recurrence in patients treated with trimethoprim/sulfamethoxazole during the maintenance therapy phase [36].

27.5 Conclusion

Staphylococcus, particularly *S. aureus*, is a highly resilient bacterium of frequent colonization in humans and associated with highly lethal diseases, especially in individuals with risk factors. Strain identification in relation to methicillin resistance is an important factor for treatment, as well as the identification of the infection origin. Bloodstream infections should be considered clinically important (they are sources of metastatic infections). Risk factors for these infections are persistence of fever for more than 71–96 h after the start of specific antibiotic therapy (especially endocarditis). Eradication of the portal of entry and infectious outbreaks is crucial. *S aureus* bacteremia can be classified as complicated (treatment duration of 4–6 weeks) and uncomplicated (exclusion of endocarditis, negative cultures after 2–4 days after start of antibiotic therapy, absence of evidence of metastatic infection, with proposed treatment of 2 weeks) [37].

References

1. Wertheim HF, Melles DC, Vos MC, et al. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. 2005;5(12):751–62.
2. Horn J, Stelzner K, Rudel T, Fraunholz M. Insidejob: staphylococcus aureus host pathogen interaction. Int J Med Microbiol. 2017;pii: S1438-4221(17):30316–8.
3. Laupland KB. Incidence of bloodstream infection: a review of population-based studies. Clin Microbiol Infect. 2013;19(6):492–500.
4. Timsit JF, Laupland KB. Update on bloodstream infections in ICUs. Curr Opin Crit Care. 2012;18(5):479–86.
5. Shurland S, Zhan M, Bradham DD, Roghmann MC. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible Staphylococcus aureus. Infect Control Hosp Epidemiol. 2007;28:273–9.
6. Hiramatsu K, Aritaka N, Hanaki H, et al. Dissemination in Japanese hospitals of strains of Staphylococcus aureus heterogeneously resistant to vancomycin. Lancet. 1997;350(9092):1670–3.
7. Siddiqui AH, Whitten RA. Methicillin resistant Staphylococcus aureus (MRSA). StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2018 Feb 22.
8. Vandecasteele SJ, Boelaert JR, De Vriese AS. Staphylococcus aureus infections in hemodialysis: what a nephrologist should know. Clin J Am Soc Nephrol. 2009;4(8):1388–400.
9. Kallen AJ, Mu Y, Bulens S, et al. Health care-associated invasive MRSA infections, 2005–2008. JAMA. 2010;304:641–8.
10. Nielsen LH, Jensen-Fangel S, Benfield T, et al. Risk and prognosis of Staphylococcus aureus bacteremia among individuals with and without end-stage renal disease: a Danish, population-based cohort study. BMC Infect Dis. 2015;15:6.
11. Lessa FC, Mu Y, Ray SM, Dumyati G, et al. Impact of USA300 methicillin-resistant Staphylococcus aureus on clinical outcomes of patients with pneumonia or central line-associated bloodstream infections. Clin Infect Dis. 2012;55(2):232–41.

12. Vanholder R. Central vein hemodialysis catheters and infection: a plea for timely referral and appropriate hygienic measures. Acta Clin Belg. 2003;58(6):342–4.
13. Lederer SR, Riedelsdorf G, Schiffl H. Nasal carriage of methicillin-resistant Staphylococcus aureus: the prevalence, patients at risk and the effect of elimination on outcomes among out-clinic haemodialysis patients. Eur J Med Res. 2007;12(7):284–8.
14. D'Agata EMC. Addressing the problem of multidrug-resistant organisms in dialysis. Clin J Am Soc Nephrol. 2018;13(4):666–8.
15. Pop-Vicas A, Strom T, D'Agata EMC. Multidrug-resistant gram-negative bacilli among chronic hemodialysis patients. Clin J Am Soc Nephrol. 2008;3:752–8.
16. Centers for Disease Control and Prevention. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recomm Rep. 2001;50:1–43.
17. Grothe C, Taminato M, Belasco A, et al. Prophylactic treatment of chronic renal disease in patients undergoing peritoneal dialysis and colonized by Staphylococcus aureus: a systematic review and meta-analysis. BMC Nephrol. 2016;17(1):115.
18. Aktaş E, Pazarli O, Külah C, Cömert F, Külah E, Sümbüloğlu V. Determination of Staphylococcus aureus carriage in hemodialysis and peritoneal dialysis patients and evaluation of the clonal relationship between carriage and clinical isolates. Am J Infect Control. 2011;39:421–5.
19. Kellum JA, Prowle JR. Paradigms of acute kidney injury in the intensive care setting. Nat Rev Nephrol. 2018;14(4):217–30.
20. Parmar A, Langenberg C, Wan L, et al. Epidemiology of septic acute kidney injury. Curr Drug Targets. 2009;10(12):1169–78.
21. Tillmann B, Wunsch H. Epidemiology and outcomes. Crit Care Clin. 2018;34:15–27.
22. Sakhuja A, Nanchal RS, Gupta S, et al. Trends and outcomes of severe sepsis in patients on maintenance dialysis. Am J Nephrol. 2016;43(2):97–103.
23. Prescott HC, Langa KM, Iwashyna TJ. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. JAMA. 2015;313(10):1055–7. Prescott HC, Angus DC. Enhancing recovery from sepsis: a review. JAMA. 2018;319(1):62–75.
24. Bartz RR, Fu P, Suliman HB, et al. Staphylococcus aureus sepsis induces early renal mitochondrial DNA repair and mitochondrial biogenesis in mice. PLoS One. 2014;9(7):e100912.
25. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375(2):122–33.
26. Fani F, Regolisti G, Delsante M, et al. Recent advances in the pathogenetic mechanisms of sepsis-associated acute kidney injury. J Nephrol. 2018;31(3):351–9.
27. Luque Y, Mesnard L. Vancomycin nephrotoxicity: frequency and mechanistic aspects. Nephrol Ther. 2018;14(Suppl 1):S133–8.
28. Elbarbry F. Vancomycin dosing and monitoring: critical evaluation of the current practice. Eur Eur J Drug Metab Pharmacokinet. 2018;43(3):259–68.
29. Kronbichler A, Kerschbaum J, Mayer G. The influence and role of microbial factors in autoimmune kidney diseases: a systematic review. J Immunol Res. 2015;2015:858027.
30. Koyama A, Kobayashi M, Yamaguchi N, et al. Glomerulonephritis associated with MRSA infection: a possible role of bacterial superantigen. Kidney Int. 1995;47:207–16.
31. Nasr SH, Fidler ME, Valeri AM, et al. Postinfectious glomerulonephritis in the elderly. J Am Soc Nephrol. 2011;22(1):187–95.
32. Wang SY, Bu R, Zhang Q, et al. Clinical, pathological, and prognostic characteristics of glomerulonephritis related to staphylococcal infection. Medicine (Baltimore). 2016;95(15):e3386.
33. Stegeman CA, Cohen Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CGM. Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. Ann Intern Med. 1994;120(1):12–7.
34. Popa ER, Stegeman CA, Abdulahad WH, et al. Staphylococcal toxic-shock-syndrometoxin-1 as a risk factor for disease relapse in Wegener's granulomatosis. Rheumatology. 2007;46(6):1029–33.
35. Radhakrishnan J, Cattran DC. The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines—application to the individual patient. Kidney Int. 2012;82(8):840–56.
36. Stegeman CA, Cohen Tervaert JW, de Jong PE, et al. Trimethoprim-sulfamethoxazole (cotrimoxazole) for the prevention of relapses of Wegener's granulomatosis. N Engl J Med. 1996;335:16–20.
37. Jung N, Rieg S. Essentials in the management of S. aureus bloodstream infection. Infection Aug. 2018;46(4):441–2.

Leprosy Nephropathy

28

Verônica Verleine Hörbe Antunes, Elvino Barros, Geraldo Bezerra da Silva Junior, Alice Maria Costa Martins, Gdayllon Cavalcante Meneses, Elizabeth De Francesco Daher, João Filipe Cavalcante Uchoa Furtado, Pedro Vianna Caldas Ribeiro, Ariana Custódio Vieira, and Juliana Hickmann de Moura

28.1 Introduction

Leprosy is a chronic disease caused by *Mycobacterium leprae*, an acid-fast bacillus of intracellular localization, highly disabling, with systemic involvement in some patients [1–3]. It has been reported as one of the oldest diseases known to humankind. The time of its appearance is not known, but it is mentioned even in the Bible [4]. *M. leprae* was described in 1873 by the Norwegian physician Amauer Hansen. It is an acid-fast bacillus, an intracellular parasite, with a preference for the Schwann cells and skin [1, 2].

28.2 Epidemiology

According to data from the World Health Organization (WHO), there is a record of leprosy in 138 countries, with an estimated worldwide prevalence of 2.2 cases per 100,000 inhabitants in 2019. The number of new cases in 2019 was 202,185 cases (2.59 cases per 100,000 inhabitants), which indicates continued transmission of the infection. Global leprosy statistics also indicate that only 14 countries, including Brazil, are responsible for over 1000 new cases per year, with only 6% of new cases being reported in the rest of the world [5]. Brazil and India are the world leaders regarding the number of leprosy cases worldwide [5]. The most recent epidemiological data from Brazil (period from 2017 to 2021) report the recording of 119,698 new leprosy cases in the country, of which 55.7% were males and 54.4% were 30–59 years old. The regions with the highest detection rates were the Midwest (37.2 cases/100,000 inhabitants) and

V. V. H. Antunes · E. Barros · A. C. Vieira · J. H. de Moura
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul. Porto Alegre, Rio Grande do Sul, Brazil
e-mail: vantunes@hcpa.edu.br

G. Bezerra da Silva Junior (✉) · J. F. C. U. Furtado · P. V. C. Ribeiro
School of Medicine, Universidade de Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

A. M. C. Martins · G. C. Meneses
Pharmaceutical Sciences Graduate Program, Universidade Federal do Ceara, Fortaleza, Ceara, Brazil

E. De Francesco Daher
Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_28

North regions (34.2 cases per 100,000 inhabitants) [6]. From 2012 to 2021 there was a significant reduction in the number of new cases (approximately 50%), from 17.17 to 8.59 new cases per 100 thousand inhabitants in 2021, showing an improvement in disease control in our country, but the number of cases remains high. In 2001, there were 68,812 active cases and in 2021, 22,426 [7].

28.3 Pathophysiology

M. leprae has a slow growth and a long incubation period, from 2 to 12 years, has a high infectivity power, and low pathogenicity. Transmission occurs from person to person via respiratory secretion, which is the main route of disease transmission. *M. leprae* infection leads to a chronic granulomatous inflammation in the skin and peripheral nerves [1, 2, 8]. Single-nucleotide polymorphisms show low alpha lymphotoxin production as a risk for disease development. Other polymorphisms have been suggested as being associated with disease development, involving other genes such as: vitamin-D receptor, TNF-alpha, interleukin 10, and HLA genes [2, 8]. The type of leprosy that the patient develops is determined by their cell-mediated immune response. The patient with the tuberculoid disease has good cell-mediated immune response and few lesions with bacilli. Patients with the lepromatous form (also known as Virchowian) have multiple lesions with the presence of mycobacteria. Schwann cells are the main target for *M. leprae* infection, leading to nerve damage, demyelination, and consequent disability. The inflammation present in the nerves is mediated by mycobacterial antigens, which activates the cell-mediated immune response by cells such as CD4+ and macrophages [2, 8].

28.4 Clinical Manifestations

The disease is mainly characterized by integumentary and peripheral nervous system lesions. The clinical picture is variable, being determined by the reaction of the host immune system to the bacillus. During the course of the disease, the so-called "reaction states" occur, during which the immune system acts against the bacillus exacerbating the clinical manifestations, which comprise two types: reverse reaction (or type I), more common in paucibacillary forms, and erythema nodosum (or type II), more common in multibacillary forms [2, 3, 8]. Currently, the disease is divided into four forms according to the World Health Organization (WHO) criteria: (1) undetermined, (2) tuberculoid, (3) dimorphic, (4) Virchowian.

The diagnosis and classification are based on clinical findings and complementary exams, performed through bacilloscopic analysis of the lesion, allowing the classification of patients into multibacillary and paucibacillary groups [3, 8].

28.4.1 Renal Impairment

Renal impairment in leprosy was first described in the beginning of the twentieth century in autopsy studies, with findings of glomerulopathies and tubular alterations [9, 10]. Leprosy-specific renal alterations have been described, including the presence of epithelioid granuloma and Hansen's bacillus in the renal parenchyma [2]. The most common renal pathologies found on biopsies of leprosy patients are glomerulonephritis, nephrosclerosis, tubulointerstitial nephritis, amyloidosis, and granulomas. However, most patients only have asymptomatic urinary abnormalities [17].

Renal lesions are found in all forms of leprosy, being more frequent in the Virchowian (multibacillary) form [11, 12]. The incidence of glomerulonephritis in leprosy ranges from 6% to 50%. Mesangial proliferative glomerulonephritis is the most common lesion in leprosy. Other forms can also be found: acute diffuse glomerulonephritis, membranous glomerulonephritis, several forms of proliferative glomerulonephritis, rapidly progressive glomerulonephritis, focal glomerulonephritis, and minimal change disease. Neutrophil inflammatory infiltrate with electrodense deposits of immune complexes in the sub-

endothelial space and capillary occlusion have also been described in leprosy. Chronic tubulointerstitial nephritis may also occur, with variable incidence, being documented in up to 71% of patients in some studies [2].

Renal amyloidosis is mainly found in the Virchowian form with an incidence ranging from 2% to 55% [2, 13], as shown in Fig. 28.1. It shows elevated proteinuria and may lead to the development of chronic kidney disease. The kidneys are the most affected organs in secondary amyloidosis that develops in leprosy.

The exact mechanism leading to the development of leprosy-associated glomerulopathy is not completely understood. *M. leprae* does not seem to be directly involved, although it has been found in some patients' glomeruli. The glomerular lesion is probably due to immunological mechanisms. Serum complements decrease and immune complex deposition in the glomerular basement membrane and in the subendothelial and subepithelial regions have been demonstrated, as observed by electron microscopy [14–16]. Other studies have detected mesangial proliferation and the presence of IgA in the mesangial region [17]. Oxidative stress also seems to play an important role in leprosy nephropathy, as demonstrated by clinical studies, which have identified elevated levels of new urinary biomarkers in leprosy patients. The levels of monocyte chemoattractant protein-1 (MCP-1) are significantly higher in the urine of leprosy patients and have a positive correlation with bacillary load and microalbuminuria, suggesting that

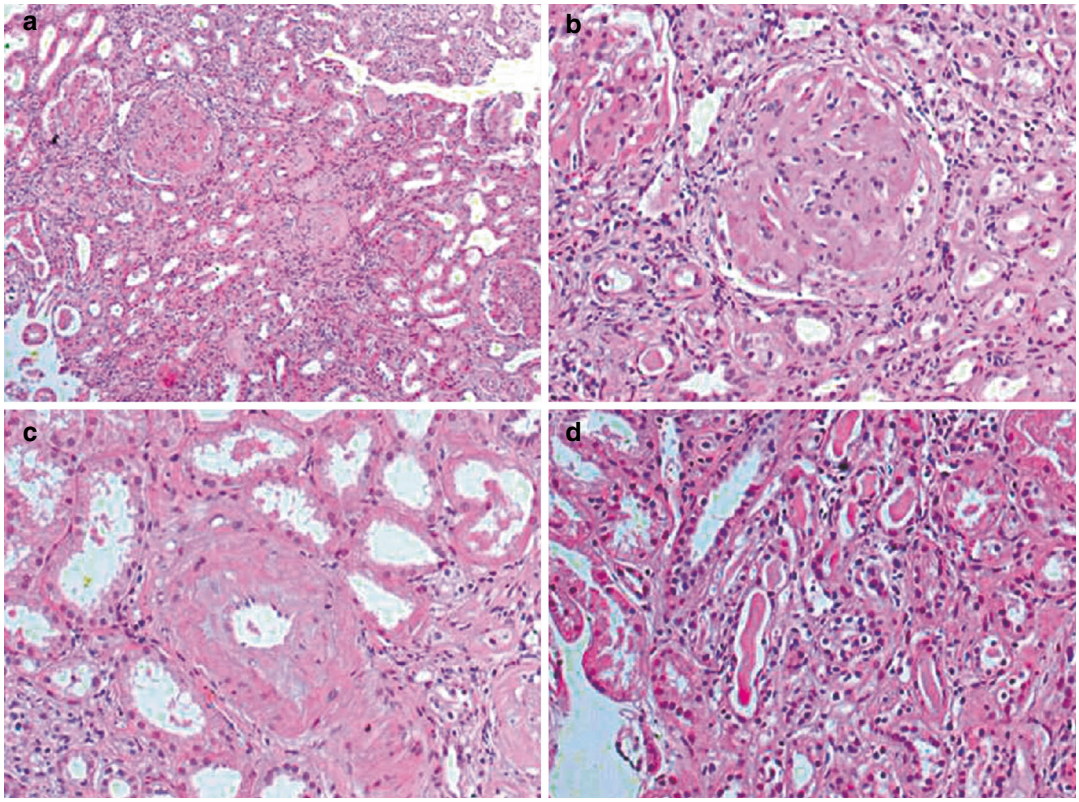


Fig. 28.1 Renal biopsy of a patient with chronic kidney disease and leprosy. (**a**) Amyloid deposits (H&E, 200x), (**b**) Glomerulus showing amyloid protein deposit in the mesangium (H&E, 400x), (**c**) Amyloid deposit (H&E, 200x), (**d**) Tubules showing no alterations (H&E, 200x). (Reproduced from Silva Junior et al. [13], with permission. © 2010 Sociedade Brasileira de Medicina Tropical)

M. leprae infection triggers a pro-inflammatory state in the renal system and represents by itself a risk of renal function loss [18].

In a clinical study carried out with 59 leprosy patients, changes in glomerular and tubular function were found [19]. Reduction of glomerular filtration rate (GFR) has been observed in some series in approximately 50% of cases. Patients with the multibacillary form had significantly lower GFR and urinary concentration capacity than those with the paucibacillary forms [19]. Urinary acidification deficit is found in 1/3 of paucibacillary and multibacillary cases. Reduced urinary concentration capacity is found in more than 2/3 of cases [19]. Urinalysis findings such as leukocyturia and hematuria are present in approximately 10% of cases and microalbuminuria in 5–8% [11, 12, 20]. Older age, disease duration, time of treatment, and the multibacillary form are risk factors for GFR decrease in patients with leprosy in the long term [11, 12].

Acute kidney injury (AKI) has been associated with leprosy glomerulonephritis and acute tubular necrosis secondary to other phenomena, such as ischemic injury or nephrotoxicity caused by drugs used in the treatment, such as rifampin and nonsteroidal anti-inflammatory drugs (NSAIDs) [11, 17]. Recurrent nodular erythema is often identified in patients who develop AKI. Chronic kidney disease can be attributed to amyloidosis or the progression of glomerular and interstitial alterations [2, 13].

A recent clinical study has shown that leprosy nephropathy has shown a trend toward being milder, predominantly glomerular in origin, manifesting as microhematuria and mild proteinuria, with significant improvement after specific treatment [20].

The pathophysiology of renal impairment in leprosy is shown in Fig. 28.2.

28.4.2 Treatment

The treatment of leprosy includes specific chemotherapy, suppression of reaction outbreaks, prevention of physical disabilities, physical and psychosocial rehabilitation. This set of measures should be developed in public or private health services by notifying the qualified health authority about the cases.

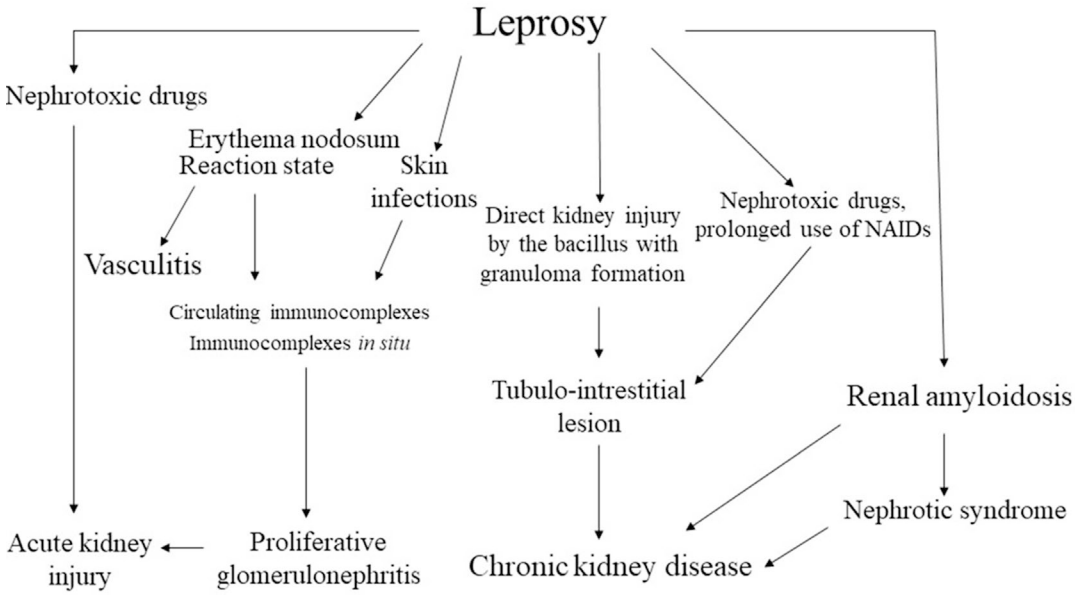


Fig. 28.2 Pathophysiology of renal involvement in leprosy. (Adapted from Daher and Silva Junior [21]. © 2018 Editora Guanabara-Koogan, Rio de Janeiro)

The drugs used in the WHO standardized regimens are rifampicin (the only bactericidal agent in the standard regimens), dapsone, and clofazimine [22]. Since 2018, the WHO started recommending the use of the three medications for the treatment of all cases of leprosy, with a duration of 6 months for paucibacillary cases and of 12 months for multibacillary cases [5, 7].

Type 1 or reversal reaction can be treated with analgesic drugs or NSAIDs when the clinical picture is mild. Patients with neuritis, extensive reaction plates on nerve pathways or at risk for ulceration should receive prednisone at a dose of 1–2 mg/kg/day until regression of the condition, when progressive reduction of corticosteroid use must start. Clinical manifestations of type 2 reaction or erythema nodosum have shown to be polymorphic and often last for months or years. The drugs used are analgesics and NSAIDs, thalidomide, clofazimine, pentoxifylline, and prednisone. Because they are potentially nephrotoxic drugs, attention should be paid to the monitoring of renal function throughout treatment.

The treatment regimens currently recommended by the Ministry of Health for paucibacillary and multibacillary patients are summarized in Tables 28.1 and 28.2.

Hemodialysis seems to have a beneficial effect on leprosy patients and advanced chronic kidney disease, increasing patient survival. Kidney transplantation may be a reasonable alternative, and the immune suppression used in transplantation does not seem to affect leprosy treatment. However, transient clinical worsening and recurrence of Virchowian leprosy have been reported after kidney transplantation.

Future perspectives in the field of leprosy include the search for new biomarkers for the early detection of nephropathy [18] and possible vaccines [23, 24]. Recent studies have shown good prospects for the development of a possible leprosy vaccine [23]. Since there is similarity between the tuberculosis bacillus and the leprosy bacillus, it is possible that vaccines can be developed based on the knowledge acquired from BCG [23].

Table 28.1 Therapeutic regimens used for the treatment of paucibacillary leprosy as recommended by the Ministry of Health, 2022

Patients >50kg	Rifampicin: 600 mg monthly dose (2 capsules containing 300 mg) under supervised administration
	Dapsone: 100 mg supervised monthly dose and 100 mg daily self-administered dose Clofazimine: 300 mg supervised monthly dose and 50 mg daily self-administered dose
Patients 30–50kg	Rifampicin: 450 mg monthly dose (1 150-mg capsule and 1 300-mg capsule) under supervised administration
Children <30kg	Dapsone: 50 mg supervised monthly dose and 50 mg daily self-administered dose Clofazimine: 150 mg supervised monthly dose and 50 mg on alternate days self-administered dose Rifampicin: 10 mg/kg once month Dapsone: 2 mg/kg supervised monthly dose and 2 mg/kg daily self-administered dose Clofazimine: 6 mg supervised monthly dose and 2 mg/kg daily self-administered dose

Source: Brazil, Ministry of Health [22]
Duration: 6 doses; follow-up of cases: monthly appointment for supervised dose; Discharge criteria: treatment will be completed with 6 supervised doses in up to 9 months; at the 6th dose, patients must undergo dermatological examination, simplified neurological assessment, and evaluation of the physical disability degree before being discharged due to cure

Table 28.2 Therapeutic regimens used for treatment of multibacillary leprosy as recommended by the Ministry of Health, 2022

Patients >50 kg	Rifampicin: 600 mg monthly dose (2 capsules containing 300 mg) under supervised administration
	Dapsone: 100 mg supervised monthly dose and 100 mg daily self-administered dose Clofazimine: 300 mg supervised monthly dose and 50 mg daily self-administered dose
Patients 30–50 kg	Rifampicin: 450 mg monthly dose (1 150-mg capsule and 1 300-mg capsule) under supervised administration
Children <30 kg	Dapsone: 50 mg supervised monthly dose and 50 mg daily self-administered dose Clofazimine: 150 mg supervised monthly dose and 50 mg on alternate days self-administered dose Rifampicin: 10 mg/kg once month Dapsone: 2 mg/kg supervised monthly dose and 2 mg/kg daily self-administered dose Clofazimine: 6 mg supervised monthly dose and 2 mg/kg daily self-administered dose

Source: Brazil, Ministry of Health [22]
Duration: 12 doses; Case follow-up: monthly appointments for supervised dose; Discharge criteria: Treatment will be completed with 12 supervised doses in up to 18 months; At the 12th dose, patients must undergo dermatological examination, simplified neurological assessment, and evaluation of the physical disability degree before being discharged due to cure. Multibacillary patients who, exceptionally, do not show clinical improvement, showing active lesions of the disease at the end of the recommended 12-dose treatment (blister packs), should be sent for evaluation at a referral service (municipal, regional, state, or national) to verify the appropriate conduct for the case

References

1. Renault CA, Ernst JD. Mycobacterium leprae. In: Mandell: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010. p. 3165–76.
2. Silva Junior GB, Daher EF, Pires Neto RJ, Pereira EDB, Meneses GC, Araújo SMHA, Barros EJG. Leprosy nephropathy: a review of clinical and histopathological features. Rev Inst Med Trop São Paulo. 2015;57(1):15–20.
3. Talhari C, Talhari S, Penna GO. Clinical aspects of leprosy. Clin Dermatol. 2015;33(1):26–37.
4. Grzybowski A, Nita M. Leprosy in the Bible. Clin Dermatol. 2016;34(1):3–7.
5. World Health Organization. Guidelines for the Diagnosis, Treatment and Prevention of Leprosy. [S. l.]: WHO, c2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf?ua=1. Accessed 1 Feb 2024.
6. Brasil, Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico—Hanseníase, n. especial, 2023. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/especiais/2023/boletim_hanseniase-2023_internet_completo.pdf. Accessed 28 Jan 2024.
7. Brasil, Ministério da Saúde. Protocolo Clínicos e Diretrizes Terapêuticas da Hanseníase. Available from https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/h/hanseniase/publicacoes/protocolo-clinico-e-diretrizes-terapeuticas-da-hanseniase-2022/. Accessed 28 Jan 2024.
8. Veronesi-Focaccia. Tratado de Infectologia. 5ª edição. ed. São Paulo: Editora Atheneu; 2015.
9. Bhandari J, Awais M, Robbins BA, et al. Leprosy. [Updated 2023 Sep 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559307/.
10. Chen KH, Lin CY, Su SB, Chen KT. Leprosy: a review of epidemiology, clinical diagnosis, and management. J Trop Med. 2022 Jul;4:2022.
11. Silva Junior GB, Daher EF. Renal involvement in leprosy: retrospective analysis of 461 cases in Brazil. Braz J Infect Dis. 2006;10(2):107–12.
12. Daher EF, Silva GB Jr, Cezar LC, Lima RS, Gurjão NH, Mota RM, et al. Renal dysfunction in leprosy: a historical cohort of 923 patients in Brazil. Trop Doct. 2011;41(3):148–50.
13. Silva Junior GB, Barbosa OA, Barros RM, dos Carvalho PR, Mendoza TR, Barreto DM, et al. Amiloidose e insuficiência renal crônica terminal associada à hanseníase. Rev Soc Bras Med Trop. 2010;43(4):474–6.
14. Grover S, Bobhate SK, Chaubey BS. Renal abnormalities in leprosy. Lepr India. 1983;55:286–91.
15. Peter KS, Vijayakumar T, Vasudevan DM, Devi KR, Mathew MT, Gopinath T. Renal involvement in leprosy. Lepr India. 1981;53:163–78.
16. Sengupta U, Ramu G, Sinha S, Ramanathan VD, Desikan KV. Immunoglobulins in the urine of leprosy patients. Int J Lepr Other Mycobact Dis. 1983;51:409–10.
17. Ozturk S, Ozturk T, Can I. Renal Involvement in leprosy: evolution of patients in Turkey. Postepy Dermatol Alergol. 2017;34(3):240–4.
18. Meneses GC, Libório AB, Daher EF, Silva Juniof GV, Costa MF, Pontes MA, Martins AM. Urinary monocyte chemotactic protein-1 (MCP-1) in leprosy

patients: increased risk for kidney damage. BMC Infect Dis. 2014;14:451.
19. Oliveira RA, Silva GB Jr, Souza CJ, Vieira EF, Mota RM, Martins AM, et al. Evaluation of renal function in leprosy: a study of 59 consecutive patients. Nephrol Dial Transplant. 2008;23(1):256–62.
20. Polito MG, Moreira SR, Nishida SK, Mastroianni KG. It is time to review concepts on renal involvement in leprosy: pre- and post-treatment evaluation of 189 patients. Ren Fail. 2015;37(7):1171–4.
21. Daher EF, Silva Junior GB. Nefropatia nas doenças tropicais. In: Riella MC, editor. Princípios de Nefrologia e Distúrbios Hidreletrolíticos. 6ª ed. Rio de Janeiro: Guanabara-Koogan; 2018. p. 553–81.
22. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Coordenação-Geral de Desenvolvimento da Epidemiologia em Serviços. Guia de Vigilância em Saúde: volume 2/Ministério da Saúde, Secretaria de Vigilância em Saúde, Coordenação-Geral de Desenvolvimento da Epidemiologia em Serviços.—1. ed. atual.—Brasília: Ministério da Saúde, 2017.
23. Coppola M, van den Eeden SJF, Robbins N, Wilson L, Franken KLMC, Adams LB, et al. Vaccines for leprosy and tuberculosis: opportunities for shared research, development, and application. Front Immunol. 2018;9:308.
24. Kumar S. India resurrects forgotten leprosy vaccine. Science. 2017;356(6342):999.

29 Leptospirosis and the Weil's Syndrome

Gabriela Studart Galdino, Geraldo Bezerra da Silva Junior, Elizabeth De Francesco Daher, Elvino Barros, Arthur Gus Manfro, Vanderlei Carlos Bertuol Junior, João Filipe Cavalcante Uchoa Furtado, and Pedro Vianna Caldas Ribeiro

29.1 Introduction

Leptospirosis remains the most pervasive zoonotic disease worldwide, disproportionately affecting resource-poor populations [1]. Its etiological agent is the spirochete bacterium belonging to the genus Leptospira. In humans, clinical manifestations exhibit a broad spectrum, ranging from mild, oligosymptomatic infections to the severe icterohemorrhagic form, also known as Weil's Syndrome. Kidney injury, characterized by acute kidney injury (AKI), is a hallmark of severe cases and is associated with increased mortality [2].

G. S. Galdino · E. De Francesco Daher
Department of Internal Medicine, Federal University of Ceara, Fortaleza, Ceara, Brazil

G. Bezerra da Silva Junior (✉) · J. F. C. U. Furtado · P. V. C. Ribeiro
School of Medicine, University of Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

E. Barros · A. G. Manfro · V. C. B. Junior
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil
e-mail: amanfro@hcpa.edu.br; vcbjunior@hcpa.edu.br

29.2 Epidemiology and Transmission

The causative agents of leptospirosis are microorganisms belonging to the genus *Leptospira*, which are obligate aerobic spirochetes widely distributed worldwide. Traditionally, the Leptospira genus was classified into two species: *L. interrogans* (pathogenic) and *L. biflexa* (nonpathogenic). However, more recent research has identified over 64 species of Leptospira, comprising 17 pathogenic, 21 intermediate, and 26 nonpathogenic species. Pathogenic species of Leptospira are further categorized based on their genotype and antigenic composition, employing serological testing methods. The serovariants within each species are delineated by the agglutination reaction of specific antibodies, and each serotype is characterized by the arrangement of epitopes on the surface-exposed lipopolysaccharide antigens [3].

Despite its global distribution, the majority of leptospirosis cases are reported in tropical and subtropical regions. This distribution is attributed to climate-related factors and the higher prevalence of poverty in these regions. Transmission primarily occurs through exposure to environmental contamination, often via contact with water tainted by the urine of infected animals (Fig. 29.1). Consequently, leptospirosis is more

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_29

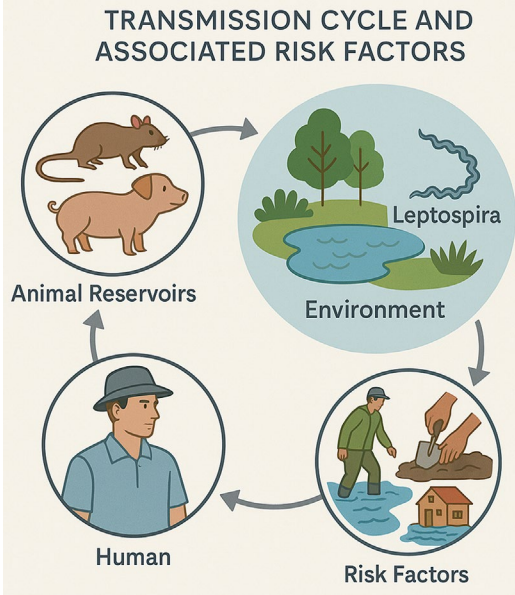


Fig. 29.1 Leptospirosis transmission cycle and associated risk factors

prevalent during rainy seasons, with epidemics frequently following floods [4]. However, transmission can also occur through direct contact with contaminated urine, blood, or tissues of infected animals. The impacts of climate change, coupled with associated natural disasters and the expansion of urban slums, have created conducive environments for the proliferation of animal reservoirs, particularly rats, thereby facilitating the spread of the disease [5].

Additionally, certain occupational groups face a notably higher risk of leptospirosis contamination, including rural workers, slaughterhouse employees, fishery workers, and veterinarians. Moreover, it is acknowledged that leptospirosis transmission can occur during recreational activities such as tourism and freshwater sports, with numerous reports of outbreaks following sports competitions [6].

Leptospirosis is a neglected disease, with its incidence often underestimated. Due to the asymptomatic or mildly symptomatic nature of most cases, many individuals do not seek medical attention or are misdiagnosed with conditions like flu or other tropical febrile syndromes such as dengue. It is estimated that over a million clinically significant cases of leptospirosis occur annually, with mortality rates hovering around 10%. Some reports suggest nearly 60,000 deaths each year [5]. Tropical regions account for three-quarters of reported cases worldwide, with South and Southeast Asia experiencing higher mortality rates. In Brazil, the infection is considered endemic and reaches epidemic proportions during the rainy season, particularly affecting densely populated areas prone to flooding and lacking proper sanitation. According to official records from the Ministry of Health, there were 3,128 reported cases of leptospirosis in 2023, resulting in 258 deaths [7].

29.2.1 Clinical Picture

Leptospirosis transmission primarily occurs through the conjunctival and oral mucosa, although it can also happen through skin lesions. Symptoms typically manifest 5–14 days after exposure [8]. Upon penetration, the spirochete disseminates hematogenously. As specific antibodies emerge, the pathogen becomes undetectable in the blood but disseminates through multiple organs and is excreted in the urine [9]. This pathogenesis underpins the classic biphasic clinical manifestation comprising leptospiremia and the immune phase. Clinical manifestations during leptospiremia are often nonspecific, with mild symptoms observed in 90% of cases. These symptoms include fever, headache, anorexia, conjunctival suffusion, diarrhea, nausea, vomiting, malaise, and myalgia, with calf pain being more pronounced [6].

In mild cases, spontaneous resolution typically occurs within 7–10 days even without antimicrobial treatment, coinciding with the emergence of antibodies. It's worth noting that the distinction between the leptospiremic and immune phases is not always clear-cut; mild cases often lack a discernible second phase, and aggressive forms of the disease can be monophasic. Although the prognosis is generally favorable, approximately 10% of patients progress to a severe form known as Weil's syndrome. Classically, this syndrome is characterized by the

triad of hemorrhagic phenomena, jaundice, and acute kidney injury [10]. The severity of leptospirosis in this condition is associated with the intensity of the host's humoral immune response [11], and mortality rates vary widely, ranging from 1% to 50%, depending on the organs affected [12].

Leptospirosis is often termed as an "infectious vasculitis." In its severe form, patients may experience hemodynamic alterations, primarily stemming from hypovolemia due to dehydration and the direct effects of toxins that damage the vascular endothelium and increase permeability. Petechiae and hemorrhages can occur in various organs, including the skin, lungs, kidneys, muscles, and brain. Pulmonary involvement in the form of alveolar hemorrhage is a hallmark of severe leptospirosis and clinically presents with symptoms such as cough, pleuritic pain, hemoptysis, and respiratory insufficiency. The pathogenesis of alveolar hemorrhage is not fully understood but is likely associated with immune complex and complement deposition in the alveolar septa, along with diffuse endothelial inflammation [13]. Respiratory failure can be severe, demanding mechanical ventilation, which is an independent risk factor for death [5]. Importantly, increased mortality among ventilated patients is observed even in the absence of other components of the Weil's triad, such as acute kidney injury [14].

Jaundice is a prevalent feature in most cases of severe leptospirosis and serves as a key sign for the presumptive diagnosis of the disease. The exact mechanism is not fully elucidated, but reports indicate alterations in biliary excretion and intrahepatic cholestasis, along with spirochete infiltration in the perisinusoidal spaces, resulting in damage to biliary canaliculi [15].

The third point in Weil's triad is characterized by acute kidney injury, which will be discussed separately later in this chapter.

29.2.2 Diagnosis

Diagnosis relies on a combination of clinical presentation and epidemiological data, which is subsequently confirmed by laboratory tests. Due to the nonspecific nature of the initial symptoms, a high index of clinical suspicion is necessary, as leptospirosis often mimics other conditions such as dengue fever, hantavirus hemorrhagic fever, viral or bacterial meningitis, malaria, or viral hepatitis. The lack of accessible and practical laboratory tests poses a significant challenge for diagnosing leptospirosis. This limitation contributes to the underdiagnosis of the disease and impedes our understanding of its natural history [16].

Some laboratory findings can suggest leptospirosis, although they lack specificity. The complete blood count typically reveals leukocytosis with a left shift in neutrophils and thrombocytopenia. The biochemical panel often shows elevated direct bilirubin, a moderate increase in transaminases, and a slight elevation in alkaline phosphatase. Azotemia may be present, typically in a nonoliguric form, accompanied by hypokalemia. Urine sediment analysis may reveal leukocyturia, low-grade proteinuria, and granular casts. In cases of meningitis, cerebrospinal fluid analysis demonstrates a predominance of lymphocytes [9].

The most commonly used diagnostic tests for leptospirosis include direct observation, cultures, polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), enzyme-linked immunosorbent assay (ELISA), lateral flow assay (LFA), and microscopic agglutination test (MAT). While cultures and MAT are considered the gold standard methods for diagnosis, they are not suitable for early detection, which is crucial since complication rates tend to be higher if treatment is delayed for more than 5 days [17]. Anti-Leptospira antibodies typically become detectable only from the second week onward, as illustrated in Fig. 29.2.

A positive Polymerase Chain Reaction (PCR) result typically indicates the presence of one of the pathogenic Leptospira species in the sample. Various post-amplification analysis methods exist, some capable of identifying the Leptospira genotype or serotype. The main advantage of PCR is its ability to confirm leptospirosis in the early stages of the disease, particularly within the

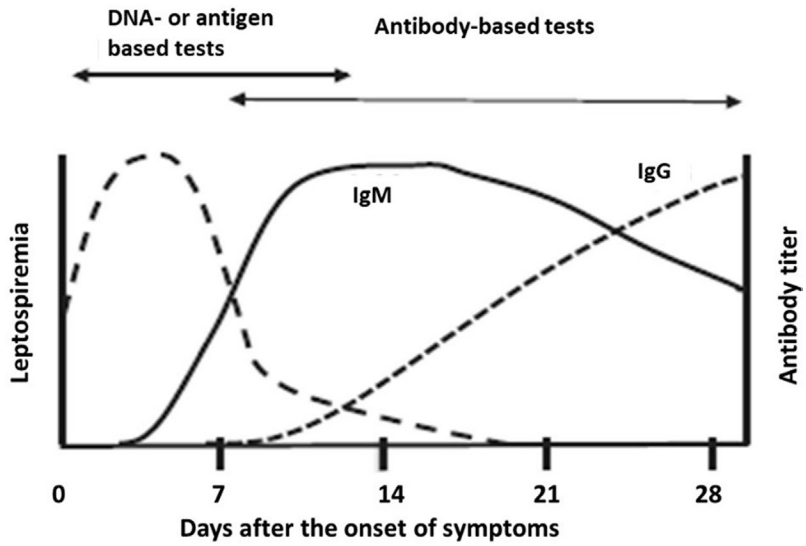


Fig. 29.2 Kinetics of leptospira infection in blood. (Adapted from Picardeau et al. [16], with permission. © 2014 Elsevier)

Table 29.1 Diagnostic tests for leptospirosis

Early detection	Microbiological methods
	Direct observation
	Culture
	Rapid nucleic acid-based test
	PCR
	LAMP
Late detection	Rapid antibody-based tests
	ELISA
	LFA
	MAT

first 5 days. Another strategy for early Leptospira identification is the use of loop-mediated isothermal amplification (LAMP); however, these tests are also costly and do not offer significant economic advantages over PCR [18].

Serologic testing is typically conducted using enzyme-linked immunosorbent assay (ELISA), lateral flow assay (LFA), and microscopic agglutination test (MAT). ELISA tests utilize surface recombinant proteins and lipoproteins of Leptospira for detection. However, due to the diversity of circulating strains, sensitivity can vary [19]. LFA is commercially available but has limited capacity to identify serovars of the icterohemorrhagiae serogroup [20].

A summary of diagnostic tests for leptospirosis is provided in Table 29.1.

29.3 Kidney Injury in Leptospirosis

The final component of Weil's syndrome is acute kidney injury (AKI), which can occur in 20–85% of patients during the second phase of the disease. Kidney complications are a hallmark of severe leptospirosis, primarily characterized by tubulointerstitial nephritis with infiltration of mononuclear inflammatory cells [21]. However, subclinical presentations can also occur, manifesting as mild proteinuria and urinary sediment alterations. Key features in the clinical presentation of AKI in leptospirosis include its nonoliguric nature and hypokalemic status. This phenomenon is attributed to the main involvement of Leptospira in the tubules and interstitium. Studies indicate that two-thirds of patients with AKI associated with leptospirosis are nonoliguric. Interestingly, reports suggest that oliguric patients have higher mortality rates [22].

Several mechanisms contribute to AKI in the context of leptospirosis. There is strong evidence supporting the direct nephrotoxic action of the microorganism and toxin effects, leading to immune response induction in the pathogenesis of AKI. Additionally, indirect effects such as dehydration, hemodynamic instability, rhabdo-

myolysis, and hypoxia play significant roles in kidney injury [21]. Acute tubular lesions can progress to interstitial edema and acute tubular necrosis. Some studies also suggest that cholestatic changes may contribute to AKI, as elevated direct bilirubin levels have been associated with oliguria in patients with severe leptospirosis.

Tubular alterations in leptospirosis are primarily degenerative and predominantly affect the proximal tubules, often occurring independently of worsening kidney function [23]. Intravascular volume depletion leading to vasomotor nephropathy may arise due to capillary injury, resulting in fluid and protein loss [12]. The hemodynamic compromise in severe cases of leptospirosis resembles the instability often seen in septic patients, where systemic vasodilation diminushes kidney perfusion [24].

The typical histological lesion observed in leptospirosis-associated kidney injury is tubulointerstitial nephritis, characterized by interstitial edema and dense local infiltrates predominantly composed of mononuclear cells. Additionally, macrophages, lymphocytes, plasma cells, and eosinophils may be present [25]. Leptospira organisms can be visualized within the renal tubules. Electron microscopy reveals stripped brush borders of tubular cells, thickening of the tubular basement membrane, and depletion of tubular cell mitochondria [26]. In chronically infected animals, kidney histopathological findings are associated with the presence of Leptospira in affected tissues (Fig. 29.3). It is also noteworthy that some reports suggest kidney lesions in leptospirosis can progress to chronic kidney disease [27].

Research into identifying early indicators of kidney injury in leptospirosis patients has led to the exploration of novel biomarkers. Notably, studies consistently highlight elevated levels of angiopoietin-2 (Angpt-2) as a significant correlation of severe disease manifestations, including acute kidney injury (AKI), sepsis, and admission to intensive care units (ICUs). Additionally, biomarkers associated with endothelial damage, particularly glycocalyx, have been implicated in kidney injury, even among individuals with mild forms of AKI. Furthermore, investigations have underscored the potential utility of urinary neutrophil gelatinase-associated lipocalin (uNGAL), plasma NGAL (pNGAL), and urinary KIM-1 markers in assessing AKI in leptospirosis patients [2].

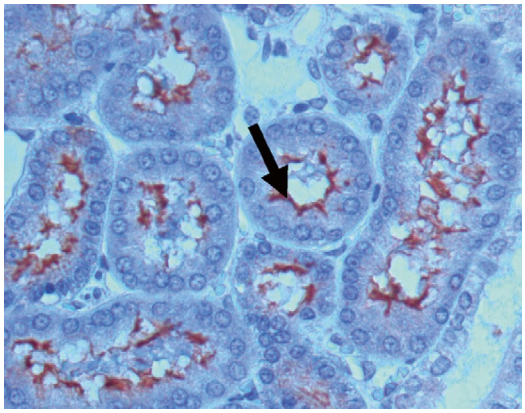


Fig. 29.3 Immunohistopathology of *Leptospira*-infected rat kidney showing *Leptospira* with specific antiserum (arrow) in the proximal tubules. (Reproduced from Adler & de la Peña Moctezuma [28])

29.4 Treatment

Timely diagnosis and prompt initiation of early supportive therapy play pivotal roles in effectively managing patients with severe forms of leptospirosis. Treatment strategies primarily focus on addressing hemodynamic instability, respiratory distress, and kidney dysfunction, often necessitating invasive interventions. Additionally, various antibiotics demonstrate in vitro activity against Leptospira, including penicillins, tetracyclines, streptomycins, azithromycin, and cephalosporins [29].

Current guidelines recommend the use of penicillin 1,500,000 units every 6 h, Ceftriaxone 1–2 grams once daily, or Cefotaxime 1 gram every 6 h for severe forms of leptospirosis. For mild outpatient cases, recommended antibiotics are Doxycycline 100 milligrams every 12 h or oral beta-lactams such as Amoxicillin 500 milligrams every 8 h. Macrolides are also an option for patients with contraindications to beta-lactams and Doxycycline. Treatment duration is 5–7 days

Table 29.2 Main studies evaluating the use of antibiotics in leptospirosis

Author, year	*n*	Antibiotic	Outcome
Costa, 2003 [38]	253	Penicillin—1 million units 4/4h for 7 days X Placebo	No difference between treatment or placebo
Daher, 2000 [39]	35	Penicillin—1 million units 4/4h for 8 days X Placebo	No difference between treatment or placebo
Edwards, 1988 [40]	79	Penicillin—2 million units 6/6h for 5 days X Placebo	No difference between treatment or placebo
Fairburn, 1956 [41]	83	Penicillin 600.000 units 6/6h for 5 days X Chloramphenicol 0.5g 6/6h for 5 days	No difference between groups
McClain, 1984 [42]	29	Doxycycline 100mg per day for 7 days X Placebo	Doxycycline reduced durations of symptoms by 2 days
Panaphut, 2003 [43]	173	Ceftriaxone 1g per day for 7 days X Penicillin 1.5 million units 6/6h for 7 days	No difference between groups
Phimda, 2007 [44]	69	Doxycycline 200mg in the first day followed by 100mg daily for 7 days X Azithromycin 1g in the first day followed by 500mg daily for 2 days	Azithromycin was not inferior to Doxycycline
Suputtamongkol, 2004 [45]	256	Penicillin 1.5 million units 6/6h for 7 days X Doxycycline 200mg followed by 100mg 12/12h for 7 days X Cefotaxime 1g 6/6h for 7 days	No difference between groups
Watt, 1988 [46]	42	Penicillin 1.5 million units 6/6h for 7 days X Placebo	Penicillin shortened hospital stay and symptoms improved faster in the treatment group

Adapted from Win TZ et al. (2024) [31]

for mild cases and at least 7 days for severe cases. Some studies suggest that Ceftriaxone use in severe infections is associated with fewer ICU admissions [30]. However, regarding mortality, no superiority of any antimicrobial agent has been demonstrated. Recent meta-analyses have questioned the efficacy of antibiotics in leptospirosis treatment, citing insufficient data [31]. These analyses found no significant differences in time to fever resolution, impact on kidney/liver function, or prognosis. However, many trials in these studies were dated and included limited patient cohorts. Table 29.2 shows the main studies evaluating the use of antibiotics in leptospirosis.

The treatment of leptospiral acute kidney injury (AKI) is a crucial part of the clinical support. A Brazilian randomized clinical trial highlighted the clinical benefits of early renal replacement therapy [32]. This trial, comparing two sustained low-efficiency dialysis (SLED) strategies, found that prompt and daily dialysis significantly improved survival in patients with Weil's syndrome requiring hemodynamic and

ventilatory support in the ICU. Furthermore, research from the same group indicated that while hemodiafiltration can reduce serum inflammatory mediators in severe leptospirosis, its impact on mortality rates remains limited [33]. Treatment strategies for leptospiral AKI vary depending on patients' metabolic and hemodynamic status and the availability of resources. Both intermittent and continuous dialysis methods, with or without hemodiafiltration, are viable options. Additionally, in settings where hemodialysis centers are scarce, peritoneal dialysis serves as a valuable alternative.

Preventing leptospirosis remains a significant challenge. Antimicrobial prophylaxis is recommended for individuals with a high likelihood of exposure to leptospires within a defined period. Although Doxycycline is the most commonly used antibiotic agent for prophylaxis, azithromycin and penicillin are also viable options. However, recent meta-analyses suggest that antimicrobial prophylaxis has limited to no effect on laboratory-confirmed leptospirosis and mortality, with the evidence certainty being low [34, 35]. Vaccination strategies have also faced hurdles in clinical applications, primarily due to low efficacy, multiple side effects, poor immune memory, and the lack of cross-protection against different Leptospira spp serovariants [36, 37].

References

1. Goldman L, Cooney KA. Goldman-Cecil medicine e-book. Elsevier Health Sciences; 2023.
2. Uribe-Restrepo P, Munoz-Zanzi C, Agudelo-Flórez P. Kidney injury biomarkers in leptospirosis. Rev Soc Bras Med Trop. 2023;56
3. Adler B. Leptospira and Leptospirosis. Springer; 2014.
4. Haake DA, Levett PN. Leptospirosis in humans. Curr Top Microbiol Immunol. 2015;387:65–97.
5. Costa F, et al. Global morbidity and mortality of leptospirosis: a systematic review. PLoS Negl Trop Dis. 2015;9:e0003898.
6. Karpagam KB, Ganesh B. Leptospirosis: a neglected tropical zoonotic infection of public health importance-an updated review. Eur J Clin Microbiol Infect Dis. 2020;39:835–46.
7. Situação Epidemiológica. Ministério da Saúde https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/l/leptospirose/situacao-epidemiologica
8. Bharti AR, et al. Leptospirosis: a zoonotic disease of global importance. Lancet Infect Dis. 2003;3:757–71.
9. De Brito T, da Silva AMG, Abreu PAE. Pathology and pathogenesis of human leptospirosis: a commented review. Rev Inst Med Trop Sao Paulo. 2018;60:e23.
10. Lomar AV, Diament D, Torres JR. Leptospirosis in Latin America. Infect Dis Clin North Am. 2000;14:23–39.
11. Daher EDF, de Abreu KLS, da Silva Junior GB. Leptospirosis-associated acute kidney injury. J Bras Nefrol. 2010;32:400–7.
12. Dassanayake DLB, et al. Predictors of the development of myocarditis or acute renal failure in patients with leptospirosis: an observational study. BMC Infect Dis. 2012;12:4.
13. da Medeiros FR, Spichler A, Athanazio DA. Leptospirosis-associated disturbances of blood vessels, lungs and hemostasis. Acta Trop. 2010;115:155–62.
14. Cruz LS, Vargas R, Lopes AA. Leptospirosis: a worldwide resurgent zoonosis and important cause of acute renal failure and death in developing nations. Ethn. Dis. 2009;19:S1-37–41.
15. Miyahara S, et al. Destruction of the hepatocyte junction by intercellular invasion of Leptospira causes jaundice in a hamster model of Weil's disease. Int J Exp Pathol. 2014;95:271–81.
16. Picardeau M, et al. Rapid tests for diagnosis of leptospirosis: current tools and emerging technologies. Diagn Microbiol Infect Dis. 2014;78:1–8.
17. Dassanayake DLB, et al. Evaluation of surveillance case definition in the diagnosis of leptospirosis, using the microscopic agglutination test: a validation study. BMC Infect Dis. 2009;9:48.
18. Yang B, et al. Nucleic acid and antigen detection tests for leptospirosis. Cochrane Database Syst Rev. 2019;8:CD011871.
19. Levett PN. Usefulness of serologic analysis as a predictor of the infecting serovar in patients with severe leptospirosis. Clin Infect Dis. 2003;36:447–52.
20. Smythe LD, et al. The microscopic agglutination test (MAT) is an unreliable predictor of infecting Leptospira serovar in Thailand. Am J Trop Med Hyg. 2009;81:695–7.
21. Chou L-F, et al. Leptospirosis kidney disease: evolution from acute to chronic kidney disease. Biomed. J. 2023;46:100595.
22. Daher EF, et al. Predictors of oliguric acute kidney injury in leptospirosis. A retrospective study on 196 consecutive patients. Nephron Clin Pract. 2009;112:c25–30.
23. Chierakul W, et al. Activation of the coagulation cascade in patients with leptospirosis. Clin Infect Dis. 2008;46:254–60.

24. Siriwanij T, et al. Haemodynamics in leptospirosis: effects of plasmapheresis and continuous venovenous haemofiltration. Nephrology. 2005;10:1–6.
25. Araujo ER, et al. Acute kidney injury in human leptospirosis: an immunohistochemical study with pathophysiological correlation. Virchows Arch. 2010;456:367–75.
26. Abdulkader RCRM, Silva MV. The kidney in leptospirosis. Pediatr Nephrol. 2008;23:2111–20.
27. Carrillo-Larco RM, Altez-Fernandez C, Acevedo-Rodriguez JG, Ortiz-Acha K, Ugarte-Gil C. Leptospirosis as a risk factor for chronic kidney disease: a systematic review of observational studies. PLoS Negl Trop Dis. 2019;13:e0007458.
28. Adler B, de la Peña Moctezuma A. Leptospira and leptospirosis. Vet Microbiol. 2010;140:287–96.
29. Griffith ME, Hospenthal DR, Murray CK. Antimicrobial therapy of leptospirosis. Curr Opin Infect Dis. 2006;19:533–7.
30. Daher EDF, et al. Risk factors for intensive care unit admission in patients with severe leptospirosis: a comparative study according to patients' severity. BMC Infect Dis. 2016;16:40.
31. Win TZ, et al. Antibiotics for treatment of leptospirosis. Cochrane Database Syst Rev. 2024;3:CD014960.
32. Andrade L, Cleto S, Seguro AC. Door-to-dialysis time and daily hemodialysis in patients with leptospirosis: impact on mortality. Clin J Am Soc Nephrol. 2007;2:739–44.
33. Cleto SA, et al. Hemodiafiltration decreases serum levels of inflammatory mediators in severe leptospirosis: a prospective study. PLoS One. 2016;11:e0160010.
34. Guzmán Pérez M, et al. Current evidence on the antimicrobial treatment and chemoprophylaxis of human leptospirosis: a meta-analysis. Pathogens. 2021;10
35. Win TZ, et al. Antibiotic prophylaxis for leptospirosis. Cochrane Database Syst Rev. 2024;3:CD014959.
36. Silveira MM, et al. DNA vaccines against leptospirosis: a literature review. Vaccine. 2017;35:5559–67.
37. Barazzone GC, et al. Revisiting the development of vaccines against pathogenic Leptospira: innovative approaches, present challenges, and future perspectives. Front Immunol. 2021;12:760291.
38. Costa E, et al. Penicillin at the late stage of leptospirosis: a randomized controlled trial. Rev Inst Med Trop Sao Paulo. 2003;45:141–5.
39. Daher EF, Nogueira CB. Evaluation of penicillin therapy in patients with leptospirosis and acute renal failure. Rev Inst Med Trop Sao Paulo. 2000;42:327–32.
40. Edwards CN, Nicholson GD, Hassell TA, Everard CO, Callender J. Penicillin therapy in icteric leptospirosis. Am J Trop Med Hyg. 1988;39:388–90.
41. Fairburn AC, Semple SJ. Chloramphenicol and penicillin in the treatment of leptospirosis among British troops in Malaya. Lancet. 1956;270:13–6.
42. McClain JB, Ballou WR, Harrison SM, Steinweg DL. Doxycycline therapy for leptospirosis. Ann Intern Med. 1984;100:696–8.
43. Panaphut T, Domrongkitchaiporn S, Vibhagool A, Thinkamrop B, Susaengrat W. Ceftriaxone compared with sodium penicillin g for treatment of severe leptospirosis. Clin Infect Dis. 2003;36:1507–13.
44. Phimda K, et al. Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. Antimicrob Agents Chemother. 2007;51:3259–63.
45. Suputtamongkol Y, et al. An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis. Clin Infect Dis. 2004;39:1417–24.
46. Watt G, et al. Placebo-controlled trial of intravenous penicillin for severe and late leptospirosis. Lancet. 1988;1:433–5.

30 Acute Kidney Injury in Tetanus

Geraldo Bezerra da Silva Junior,
Juliana Gomes Ramalho de Oliveira,
Guilherme Alves de Lima Henn, Gustavo Mandelli,
Pedro Guimarães Pascoal,
João Filipe Cavalcante Uchoa Furtado,
Pedro Vianna Caldas Ribeiro,
and Elizabeth De Francesco Daher

30.1 Introduction

Tetanus is a noncommunicable, immune-preventable, acute infectious disease that can be fatal in many cases, It is caused by neurotoxins produced by *Clostridium tetani*, an anaerobic sporulated gram-positive bacillus that has spores, which ensure long-term survival in the environment [1, 2]. It is characterized by central nervous system (CNS) hyperexcitability, muscular stiffness (initially located in the mandible, neck, and later generalized) accompanied by musculoskeletal spasms [1, 2]. Also known as tonic seizures, these spasms are responsible for most deaths and can be triggered by light stimuli, patient handling, coughing, and swallowing, among others [3–8].

The first descriptions of tetanus infection were recorded in mid-1500 BC. However, in 640 BC, Hippocrates differentiated between the generalized and localized forms and concluded that a tetanus patient that survived the fourth day of the disease would have a better prognosis [3]. During World War I, passive immunization in humans was used as treatment and prophylaxis after Nocard's discoveries about the protective effect of the passively transferred antitoxin in 1897. In the early 1920s, Ramon developed a method to inactivate the tetanus toxin with formaldehyde, which later, in 1924, contributed to the development of the tetanus toxoid by Descombey, which was first used during World War II [1].

The infection occurs through superficial or deep wounds used as spore entry ports for contact with continuity solution in the skin and mucosa [2]. Overall, tetanus infection has four clinical presentations: localized, when it is concentrated in the lesions; cephalic, a rare form that may be related to head injury or infections such as otitis media; generalized, which accounts for approximately 80% of cases; and neonatal tetanus, which affects newborns in the first 28 days of life whose mothers did not receive prenatal tetanus vaccine

G. Bezerra da Silva Junior (✉) · J. G. R. de Oliveira · J. F. C. U. Furtado · P. V. C. Ribeiro
School of Medicine, University of Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

G. A. de Lima Henn
Department of Community Health, Federal University of Ceara, Fortaleza, Ceara, Brazil

G. Mandelli · P. G. Pascoal
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil
e-mail: gmandelli@hcpa.edu.br; ppascoal@hcpa.edu.br

E. De Francesco Daher
Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_30

[1]. Tetanus can also be clinically classified as neonatal and accidental [3].

Although rare in countries with healthcare resources, tetanus can still be a threat to those unvaccinated, especially in poorer regions. Since it is not possible to eradicate *C. tetani* spores from the environment, specific immunization and care for wounds and traumatic injuries are the highlights of prevention [25].

30.2 Epidemiology

Although uncommon in countries with access to healthcare resources, especially after the incorporation of vaccination into childcare in the 1940s, tetanus continues to be endemic in regions with low socioeconomic development [26]. Because it is not a notifiable disease in many countries [11–16], it is challenging to estimate the true burden represented by accidental tetanus, considered the one that occurs outside the neonatal period [3].

Even with a more well-structured healthcare system through the years, there is evidence of an increase in disease incidence following natural events and conflicts worldwide. It is believed that this occurs due to the rise in injuries that predispose to infection, population migration, and interruption in vaccination programs [28].

Most cases arise in individuals with incomplete immunization who did not complete adequate prophylaxis after exposure [31, 32]. It may be associated with increased exposure of male to trauma, related to occupational risk or not, and low utilization of health services, resulting in a predominance of infection incidence in this gender [3]. On the other hand, females have more access to tetanus immunization due to prenatal care, which includes a dose of dTpa vaccine (diphtheria, tetanus, and pertussis) at each pregnancy [2].

Vaccination stimulates production of IgG antibodies, but over time, seric levels decrease, turning a booster dose essential. Elderly are at higher risk of infection, either due to declining antibody titers or because they were born before the introduction of vaccination programs [27].

Among the risk groups are also intravenous drug users, since subcutaneous or intramuscular injections favor infection by anaerobic bacterias [29, 30].

Diabetic patients with infected ulcers on extremities, patients with dental infections, postoperative cases involving necrotic abdominal infection by intestinal microbiota, obstetric patients after septic abortion, and neonates at risk of umbilical cord infection also constitute risk groups.

In the United States, the incidence of tetanus declined steadily after the 1940s, when vaccine was incorporated into childhood care. Between 2009 and 2012, an average of 29 cases per year were reported. Regarding neonatal tetanus, only two cases have been registered since 1989 in that country [1]. According to the European Center for Disease Prevention and Control (ECDC), in 2015, 117 cases of tetanus were reported, of which 67 were confirmed in the 26 countries that comprise the European Union, with the highest prevalence in Italy (41% of cases) [5].

In recent decades, Brazil has been experiencing a decline in the number of accidental tetanus cases. According to the Ministry of Health of the Brazilian government, between the years 2012 and 2022, 2,590 cases of accidental tetanus were recorded in the country: 352 in the North Region (13.6%), 821 in the Northeast Region (31.7%), 571 in the Southeast Region (22.0%), 542 in the South Region (21.0%), and 304 in the Midwest Region (11.7%). In 2022, the incidence rate dropped to 0.05 per 100,000 inhabitants, compared to 0.16 in 2012. Also in 2022, 81% of the cases were concentrated among individuals aged 30 to 79 years old. Most cases occurred in retired/pensioner categories, agricultural workers, followed by groups of construction workers, students, housewives, and itinerant agricultural workers. This reduction is mainly due to the consolidation of national vaccination campaigns, internationally recognized for their distinguished results, which increased the population's access to tetanus immunization [33].

During 2021, 2022, and 2023, 173, 200, and 135 were confirmed throughout the national territory. The lethality during this same period was 27%, 26%, and 26%, respectively. Compared to countries with higher socioeconomic power, where lethality ranges between 10% and 17%, the lethality Brazil was considered high [33].

Although it is a preventable disease, tetanus still has high mortality rates in underdeveloped and developing countries due to recurrent deficiencies in tetanus immunization coverage. The population's adherence to mass vaccination campaigns is known to be influenced by individual, collective, cultural, social, and economic factors [7], and the involvement of several sectors of society is necessary to attain better results.

30.3 Pathophysiology

Through inoculation from damaged human tissue, *C. tetani* spores germinate under ideal anaerobic conditions to form the vegetative state of the bacteria. Regulated by a complex system involving intrinsic regulatory factors and environmental signals, the bacteria produce metalloprotease tetanus toxin, also known as tetanospasmin.

Highly neurotoxic, tetanus toxin attaches to presynaptic membranes at neuromuscular junctions and is then taken up and transported backward along the motor neuron. Upon reaching the spinal cord and brainstem, it is secreted and enters adjacent inhibitory interneurons, blocking neurotransmission by cleaving membrane proteins involved in neuroexocytosis [34, 35]. Consequently, inhibition of neurotransmission regulating anterior horn cells and muscle contraction occurs, resulting in increased muscle tone, painful spasms, and generalized autonomic instability.

Sweating, tachycardia, and hypertension are manifestations of a hypersympathetic state produced by the toxin through the induction of neural control loss over adrenal catecholamine release [35, 36].

These manifestations induced by the toxin are long-lasting, as recovery requires the growth of new axonal nerve terminals.

30.4 Clinical Manifestations

Although in most cases of tetanus contamination arises from small cuts or abrasions, in 20–50% of cases, no obvious entry site is found [37]. It is believed to occur because the initial injury was minor and symptoms appeared long afterward that the initial wound was no longer visible or remembered by the patient. In children older than 1 month, middle ear infection is a common entry point; in neonates, it is usually through the umbilical cord [38].

The incubation period, the time from the initial injury to the onset of the first symptoms, ranges from 3 to 21 days. This period is commonly shorter in neonates, sometimes occurring within hours. However, the severity of the disease seems to be more related to the speed of symptom progression, with patients presenting worse prognosis if there is a shorter interval between the first symptoms and the onset of spasms—progression period [37].

Manifestations in non-neonatal tetanus are divided into three groups: local, cephalic, and generalized. In local tetanus, tonic and spastic muscle contractions occur in one extremity or region of the body. Diagnosis can be challenging, as it opens up a wide range of differential diagnoses. The local form may result from a small toxin load or as an initial manifestation of the generalized form [39].

Cephalic tetanus usually results from wounds on the neck or head, initially involving only cranial nerves, with the facial nerve being the most commonly affected. Trismus and *risus sardonicus* are consequences of facial muscle spasms, generally accompanied by dysphagia. Laryngeal and pharyngeal spasms can also occur, resulting in bronchoaspiration and airway compromise [40]. Similar to local tetanus, diagnosis is difficult and may represent an initial manifestation of generalized tetanus.

As the most common and severe form of the disease, in generalized tetanus, all muscle groups are affected, and as mentioned earlier, it may initially present as the cephalic or local form. Patients experience episodes of tonic contraction followed by prolonged muscle spasms, and since

the disease does not affect consciousness, these events are extremely painful. Spasms can be triggered by visual, auditory, or tactile stimuli, leading to characteristic findings such as neck stiffness, *risus sardonicus*, board-like abdominal rigidity, and opisthotonus. Additionally, symptoms of autonomic hyperactivity are evident, initially manifested by sweating and tachycardia. As the disease progresses, profuse sweating, cardiac arrhythmias, blood pressure instability, and fever may be present. Disturbances in intestinal function, bladder contractility, and increased respiratory secretions are also noted [40].

It is believed that recovery from the effects induced by tetanus toxin may extend from 4 to 6 weeks, as recovery will depend on the growth of new axonal nerve terminals.

Diagnosis is clinical, based on medical history, physical examination, and semiological findings, with no specific laboratory exam. The presence of antibodies at protective levels with titers above 0.1 IU/mL by ELISA test makes tetanus infection unlikely [41]. Reports of susceptible injuries and a history of inadequate immunization support the diagnosis. Consideration should be given to differential diagnoses such as drug-induced dystonias, like those by phenobarbital and metoclopramide, other causes of trismus, such as dental infections and jaw/pharyngeal pathologies, strychnine poisoning, and malignant neuroleptic syndrome.

Researchers have shown that hyperglycemia, hyperkalemia, and thrombocytopenia in the tetanus clinical picture were associated with increased mortality [16] and that there is a statistically significant association between age and the outcomes (discharge and death) [11]. In most severe cases, autonomic dysfunction with hypertension and tachycardia oscillating with bradycardia and hypotension is associated with worse prognosis [14].

30.5 Acute Kidney Injury

Evidence suggests that acute kidney injury (AKI) in tetanus infection is common, occurs early, and is associated with increased mortality [13, 17], but its pathophysiology is not yet completely understood. It is known that there is an increase in sodium and potassium excretion fraction, indicating impairment of the proximal tubule and preservation of distal portions, respectively [17].

Often mild and non-oliguric [42, 43], acute kidney injury presents multifactorial etiology suggesting various pathophysiological mechanisms involved. Among the related factors, autonomic dysfunction appears to be the most important in the development of kidney injury [42]. Hemodynamic changes involving blood pressure lability with hypertensive peaks and episodes of severe hypotension and alternating between bradycardia and tachycardia presents implications on renal perfusion; changes in bladder contractility may justify post-renal causes in those without a urinary catheter; increased urinary excretion of catecholamines may lead to variations in renal microperfusion; and muscle spasms may trigger severe muscle damage, leading to rhabdomyolysis and myoglobinuria [17].

Regarding the role of rhabdomyolysis in the genesis of kidney injury in tetanus, a study carried out in the state of Bahia, Brazil, concluded that, although AKI affected 39% of patients, there was no correlation with serum myoglobin or creatine kinase (CK) levels [20], suggesting the action of other factors and that rhabdomyolysis is not characterized as a fundamental cause of AKI in tetanus [13]. However, elevated serum CK levels and myoglobinuria are frequent clinical findings in two-thirds of tetanus cases, and it is known that glomerular filtration rate decreases in the presence of myoglobinuria [17]. Therefore, in the differential diagnosis of acute kidney injury (AKI), in a clinical picture of increased CPK and myoglobin release, tetanus should be one of the hypotheses to be considered [21].

A study found that patients with lower glomerular filtration rates had received more neuromuscular blockers, such as pancuronium, indicating a possible contribution of this class of drugs to kidney injury [22]. However, the conclusion of this study strongly suggested that the autonomic nervous system hyperactivity was the decisive factor in the glomerular filtration rate decrease in tetanus [22].

Studies have indicated that oliguria is not a common finding in cases of kidney impairment in tetanus [16, 17, 20]. Regarding the influence of AKI on lethality, a study of 85 patients in a single center in the state of Ceará, Brazil, showed that 11.8% of tetanus cases had AKI, with no statistically significant association with death [16]. However, in a study of 389 cases in Vietnam, AKI was associated with 16% of deaths [23]. In Africa, in the 1980s, kidney failure after tetanus infection was responsible for the death of 65% of the studied patients [24].

Other factors also influence the frequent presence of acute kidney injury in these patients, such as the use of nephrotoxic medications, the presence of overlapping infections leading to septic conditions, complications related to mechanical ventilation [18], and episodes of profuse sweating, which can lead to a prerenal condition due to dehydration.

The pathophysiology of AKI in tetanus is depicted in Fig. 30.1.

Regardless of the pathophysiology leading to AKI, it is essential to be attentive to external factors contributing to its aggravation and perpetuation. It is crucial that the treatment of the disease and its complications is instituted as promptly as possible. Whenever feasible, it is recommended to adjust medication doses according to glomerular filtration rate and avoid nephrotoxic drugs when viable alternatives exist. Additionally, it is imperative to monitor fluid balance by quantifying infusions, diuresis, sensible and insensible losses and avoid hypovolemia.

30.5.1 Treatment

Tetanus treatment is divided into specific and unspecific or symptomatic treatment. Specific treatment has three main objectives: to destroy the bacilli to prevent further release of toxins, to neutralize the toxin present in the body but out-

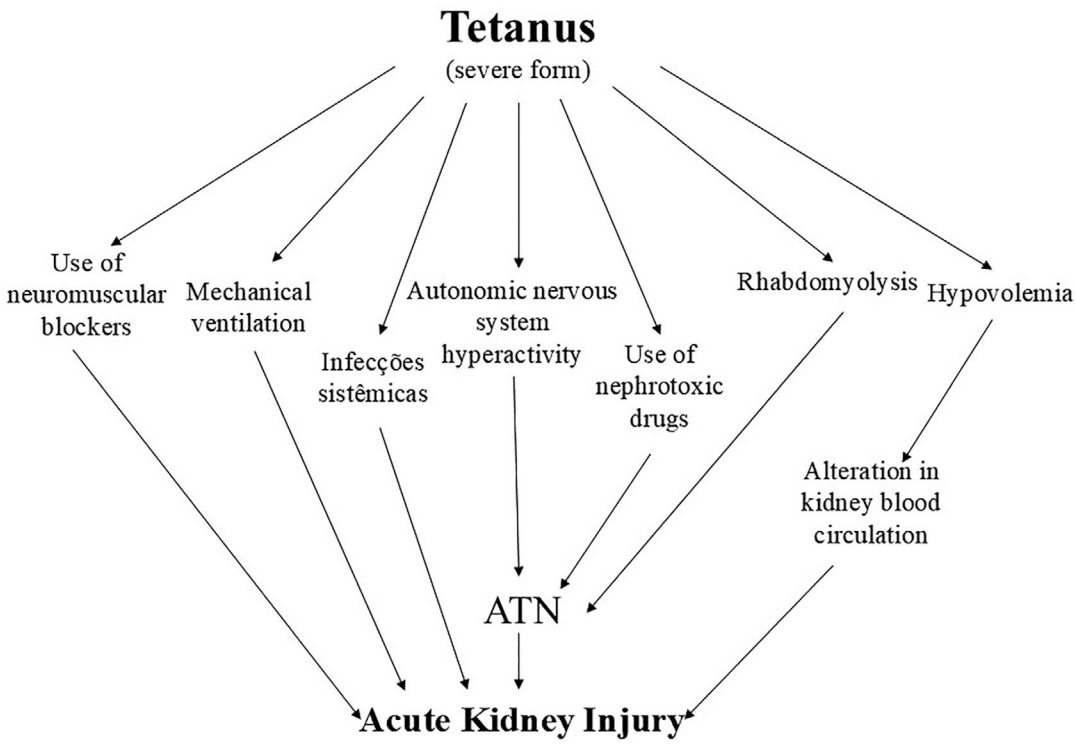


Fig. 30.1 Pathophysiology of acute kidney injury in tetanus. **ATN* acute tubular necrosis

side the central nervous system (CNS), and to minimize the effects of the toxin present in the CNS [19].

As for the nonspecific or symptomatic treatment of patients with severe tetanus, the main challenges are the control of muscle stiffness and spasms, the treatment of autonomic disorders, the prevention of complications [19], the control of opportunistic infections, and hemodynamic balance [9].

When present, proper wound management should be performed. Debridement of the injury by removing necrotic areas or foreign bodies aims to eliminate remaining spores and prevent the formation of a conducive environment for bacterial germination. Inadequate wound management may result in antimicrobial therapy failure.

Although antibiotic therapy is not central in the management of tetanus, its use is recommended. Metronidazole, at a dose of 500mg intravenously every 6–8 h, is the therapy of choice, with penicillin G, at a dose of 2–4 million units intravenously every 4–6 h, being a safe alternative. Other alternatives include: doxycycline, macrolides, clindamycin, vancomycin, and chloramphenicol [28]. Treatment is suggested to be administered for 7–10 days. Monitor for possible overlapping infections and adjust therapy as needed.

Once performed, the binding of tetanus toxin to tissue is irreversible. Through passive immunization, however, the aim is to neutralize free toxins, thereby increasing survival. Immunoglobulin (TIg) should be administered intramuscularly or intravenously, part of it around the wound. TIg is recommended for the treatment of accidental or neonatal tetanus and for the prevention of tetanus in patients with wounds at high risk. Moreover, those who are unvaccinated, with uncertain vaccination status, or with less than three doses, or those who have received three doses but the last dose was more than 10 years ago may benefit from TIg. The earlier the administration, the greater its effectiveness [44].

All patients with tetanus should be vaccinated, as the disease does not confer immunity. It is indicated in conjunction with anti-tetanus serum and should be administered at different sites. Booster doses every 10 years are recommended [44].

Control of muscle spasms is essential, as they lead to life-threatening conditions such as swallowing alterations, bronchoaspiration, muscle fatigue, and respiratory failure. Attention should be paid to environmental control, avoiding light, sound, and tactile stimuli that may trigger muscle contractions. The use of medications such as benzodiazepines and other sedatives is recommended, as they are effective in controlling stiffness and tetanic spasms. Diazepam is commonly used, and when high doses are required, switching to continuous intravenous infusion of midazolam is endorsed. Care should be taken for signs of withdrawal during the drug withdrawal process. When sedatives are not sufficient, neuromuscular blockers may be added.

Added to the above-mentioned recommendations, Magnesium sulfate is used in the management of autonomic dysfunctions. It acts as a presynaptic neuromuscular blocker, inhibiting the release of catecholamines and reducing receptor responsiveness [45–47]. Studies show that magnesium infusion has reduced the need for other drugs to control muscle spasms.

Appropriate nutritional therapy is also crucial to the treatment of the disease. Attention should also be paid to the implementation of prophylaxis, such as for stress ulcers, deep vein thrombosis, and pressure ulcers.

AKI prevention in tetanus infection is performed through close monitoring for the early diagnosis of autonomic dysfunction, effective prevention of rhabdomyolysis, strict control of urine output, glomerular filtration rate, and myoglobinuria [18].

Medical care for tetanus patients should be based primarily on permanent care and the utmost precaution in patient management and therapeutic choices in order to protect them from possible iatrogenesis [3].

30.6 Conclusions

It is impossible to dissociate the occurrence of tetanus from social, economic, and environmental factors. The preventive measures are simple and range from domestic habits, such as wearing shoes to vaccine adherence, available for free in the public health system in Brazil. Continued multisectoral efforts are needed to ensure that vaccination is systematized in underdeveloped and developing countries, so that coverage reaches the most susceptible groups.

References

1. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. Washington D.C.: Public Health Foundation; 2015.
2. Brasil, Ministério da Saúde, Secretaria de Vigilância em Saúde, Coordenação-Geral de Desenvolvimento da Epidemiologia em Serviços. Guia de Vigilância em Saúde: Volume Único [Internet]. Brasília; 2017. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/guia_vigilancia_saude_2ed.pdf
3. Focaccia R, Tavares W, Mazza CC, Veronesi R. Tétano. In: Focaccia R, editor. Tratado de Infectologia. 5th ed. São Paulo: Atheneu; 2015. p. 1373–98.
4. Unicef. Região das Américas elimina o tétano materno e neonatal [Internet]. 2017. Available from: https://www.unicef.org/brazil/pt/media_37128.html
5. European Centre for Disease Prevention and Control. Tetanus. In: ECDC Annual epidemiological report for 2015 [Internet]. Stockholm: ECDC; 2017. Available from: https://ecdc.europa.eu/en/publications-data/tetanus-annual-epidemiological-report-2015.
6. Brasil. Ministério da Saúde. Tétano Acidental - Situação Epidemiológica [Internet]. Available from: http://portalms.saude.gov.br/saude-de-a-z/tetano-acidental/11473-situacao-epidemiologica-dados
7. Feijão AR, de Brito DMS, Peres DA, Galvão MTG. Tétano acidental no Estado do Ceará, entre 2002 e 2005. 426 Rev da Soc Bras. Med Trop. 2007;40(4):426–30.
8. Neves FF, Faiolla RCL, De NEMG, De LGMN, Muniz RZDA, Pazin-Filho A. Clinical and epidemiological profile of accidental tetanus cases in Ribeirão Preto in the State of São Paulo from 1990 to 2009. Rev Soc Bras Med Trop. 2011;44(4):481–5.
9. da Nóbrega MVD, Reis RC, Aguiar ICV, Queiroz TV, Lima ACF, Pereira EDB, et al. Patients with severe accidental tetanus admitted to an intensive care unit in Northeastern Brazil: clinical–epidemiological profile and risk factors for mortality. braz j infect dis. 2016;20(5):457–61.
10. Brauner J, Vieira RS, Bleck T. Changes in severe accidental tetanus mortality in the ICU during two decades in Brazil. Intensive Care Med. 2002;28:930–5.
11. Marulappa VG, Manjunath R, Mahesh N, Maligegowda L. A ten year retrospective study on adult Tetanus at the epidemic disease (ED) hospital, Mysore in Southern India: a review of 512 cases. J Clin Diagnostic Res. 2012;6(8):1377–80.
12. Lima EQ, Silva RG, Fernandes IMM, Abbud-Filho M, Burdmann EA. Case report: tetanus-induced acute kidney injury in a renal transplant recipient. Am J Trop Med Hyg. 2007;77(2):400–2.
13. Lisboa T, Ho Y-L, Henriques Filho GT, Brauner JS, Valiatti JL dos S, Verdeal JC, et al. Diretrizes para o manejo do tétano acidental em pacientes adultos. Rev Bras Ter Intensiva. 2011;23(4):394–409.
14. World Health Organization. Current recommendations for treatment of tetanus during humanitarian emergencies [Internet]. 2010. Available from: http://www.who.int/diseasecontrol_emergencies/publications/who_hse_gar_dce_2010.2/en/
15. Gibson K, Bonaventure Uwineza J, Kiviri W, Parlow J. Tetanus in developing countries: a case series and review. Can J Anesth Can d'anesthésie. 2009;56:307–15.
16. Moura Filho JF, Mendonça PR, Lima EB, Maria J, Júnior SS, Pinho MLM, et al. Acute renal failure and other clinical features in tetanus patients from northeastern Brazil. Ann Trop Med Public Heal. 2008;1(2)
17. Daher EF, Silva Júnior GB. Nefropatia nas doenças tropicais. In: Riella M, editor. Princípios de Nefrologia e Distúrbios Hidroeletrolíticos. 6th ed. Rio de Janeiro: Guanabara-Koogan; 2018. p. 553–81.
18. Kaur S, Mishra D, Juneja M. Acute renal failure in tetanus. Indian J Pediatr. 2014;81(2):207.
19. Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. Br J Anaesth. 2001;87(3):477–87.
20. Martinelli R, Matos C, Rocha H, Eonir RH. Tetanus as a cause of acute renal failure: possible role of Rhabdomyolysis. Rev Soc Bras Med Trop. 1993;26(l):1–4.
21. Weiss MF, Badalamenti J, Fish E. Tetanus as a cause of rhabdomyolysis and acute renal failure. Clin Nephrol. 2010;73(1):64–7.
22. Daher EF, Abdulkader RCRM, Motti E, Marcondes M, Sabbaga E, Burdmann EA. Prospective study of tetanus-induced acute renal dysfunction: Role of adrenergic overactivity. Am J Trop Med Hyg. 1997;57(5):610–4.
23. An VT, Khue PM, Yen LM, Phong ND, Strobel M. Le tétanos à Hô-Chi-Minh-Ville, Vietnam : épidémiologie, clinique et pronostic, à propos de 389 cas à l'Hôpital des maladies tropicales. Bull la Soc Pathol Exot. 2015;108:342–8.
24. Seedat YK, Omar M, Seedat M, Wesley A, Pather M. Renal failure in tetanus. Br Med J. 1981;282
25. WHO. Maternal and neonatal tetanus elimination (MNTE). 2019. https://www.who.int/immunization/diseases/MNTE_initiative/en/index1.html. Accessed 12 Mar 2019

26. Centers for Disease Control and Prevention. Tetanus. https://www.cdc.gov/vaccines/pubs/surv-manual/chpt16-tetanus.html. Accessed on 24 Feb 2020
27. Weinberger B. Adult vaccination against tetanus and diphtheria: the European perspective. Clin Exp Immunol. 2017;187:93–9.
28. Afshar M, Raju M, Ansell D, Bleck TP. Narrative review: tetanus-a health threat after natural disasters in developing countries. Ann Intern Med. 2011;154:329.
29. Beeching NJ, Crowcroft N. Tetanus in injecting drug users. BMJ. 2005;330:208–9.
30. Pascual FB, McGinley EL, Zanardi LR, Cortese MM, Murphy TV. Tetanus surveillance: United States, 1998–2000. MMWR Surveill Summ. 2003;52:1–8.
31. Centers for Disease Control and Prevention (CDC). Tetanus surveillance—United States, 2001–2008. MMWR Morb Mortal Wkly Rep. 2011;60:365.
32. Yaffee AQ, Day DL, Bastin G, et al. Notes from the field: obstetric tetanus in an unvaccinated woman after a home birth delivery—Kentucky, 2016. MMWR Morb Mortal Wkly Rep. 2017;66:307.
33. Ministério da Saúde Governo do Brazil, Accidental Tetanus [internet]. 2023. Available from: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/t/tetano-acidental
34. Lalli G, Bohnert S, Deinhardt K, et al. The journey of tetanus and botulinum neurotoxins in neurons. Trends Microbiol. 2003;11:431.
35. Caccin P, Rossetto O, Rigoni M, et al. VAMP/synaptobrevin cleavage by tetanus and botulinum neurotoxins is strongly enhanced by acidic liposomes. FEBS Lett. 2003;542:132.
36. Thwaites CL, Yen LM, Glover C, et al. Predicting the clinical outcome of tetanus: the tetanus severity score. Trop Med Int Health. 2006;11:279.
37. Thwaites CL, Yen LM, Nga NT, et al. Impact of improved vaccination programme and intensive care facilities on incidence and outcome of tetanus in southern Vietnam, 1993–2002. Trans R Soc Trop Med Hyg. 2004;98:671–7.
38. Patel JC, Mehta BC. Tetanus: study of 8,697 cases. Indian J Med Sci. 1999;53:393–401.
39. Ferdinec AA, Matzke HA. The relationship of toxin and antitoxin injection site to tetanus development in the rat. J Exp Med. 1959;110:1023–40.
40. Udwadia FE. Tetanus. New York: Oxford University Press; 1994.
41. WHO. WHO immunological basis for immunization series module 3: tetanus update 2018. 2018. http://www.who.int/immunization/documents/ISBN9789241513616/en/. Accessed 10 Mar 2019
42. Daher EF, Abdulkader RC, Motti E, Marcondes M, Sabbaga E, Burdmann EA. Prospective study of tetanus-induced acute renal dysfunction: Role of adrenergic overactivity. Am J Trop Med Hyg. 1997;57:610–4.
43. Martinelli R, Matos CM, Rocha H. Tetanus as a cause of acute renal failure: Possible role of rhabdomyolysis. Rev Soc Bras Med Trop. 1993;26:1–4.
44. Instituto Butantan, dizeres de texto de bula—profissional da saúde [internet]. 2024. Available from: https://butantan.gov.br/assets/arquivos/soros-e-vacinas/2024/Bula%20Profissional%20da%20Saúde%20Soro%20Antitetânico.pdf
45. Lipman J, James MF, Erskine J, et al. Autonomic dysfunction in severe tetanus: magnesium sulfate as an adjunct to deep sedation. Crit Care Med. 1987;15:987.
46. Weiss MF, Badalamenti J, Fish E. Tetanus as a cause of rhabdomyolysis and acute renal failure. Clin Nephrol. 2010;73:64–7.
47. Asherson AP, Ruttmann TG. Severe anuric renal failure in a patient with tetanus. Br J Anaesth. 2002;88:740–1.

Renal Tuberculosis

31

Rafael Siqueira Athayde Lima,
Geraldo Bezerra da Silva Junior,
João Filipe Cavalcante Uchoa Furtado,
Pedro Vianna Caldas Ribeiro, Elvino Barros,
and Elizabeth De Francesco Daher

31.1 Introduction

Tuberculosis (TB) is a disease caused in most cases by *Mycobacterium tuberculosis*, but it can be also caused by other species of mycobacteria. The disease has become a severe public health problem since the industrial revolution in Europe, when population growth resulted in larger clusters of people in urban spaces.

31.2 Epidemiology

The incidence of TB is increasing, especially in developing countries. In 2016, 6.3 million new TB cases were reported worldwide, and 129,689 cases started treatment for multiresistant TB. The highest incidences are recorded in Southeast Asia, Africa, and the Pacific areas. TB is the ninth leading cause of death worldwide and the leading cause of death from an isolated infectious agent, being higher than HIV. In 2016, 1.3 million TB deaths were estimated in individuals without HIV and 374,000 in individuals with HIV. Many of these deaths could have been prevented with early diagnosis and adequate treatment [1].

In Brazil, over the last decade, an average of 70,000 new TB cases have been reported per year [2]. In 2016, 66,796 new cases of TB were recorded in Brazil. From 2007 to 2016, the coefficient of disease incidence had an average annual variation of −1.7%, going from 37.9/100,000 inhabitants in 2007 to 32.4/100,000 inhabitants in 2016 [3].

R. S. A. Lima
Division of Nephrology, Hospital Geral de Fortaleza, Fortaleza, Ceara, Brazil

School of Medicine, Universidade Federal do Ceara, Fortaleza, Ceara, Brazil

G. Bezerra da Silva Junior (✉) · J. F. C. U. Furtado · P. V. C. Ribeiro
School of Medicine, Universidade de Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

E. Barros
Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil

E. De Francesco Daher
Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_31

31.3 HIV and Organ Transplantation

Extrapulmonary TB cases have become more common since the appearance of the human immunodeficiency virus (HIV) and the increase in organ transplants and the consequent drug immunosuppression [4]. HIV-infected patients have a 20–37-fold higher risk of TB. In 2016, of the 6.3 million new cases recorded worldwide, 476,774 occurred in individuals with HIV [1]. TB is the most frequent opportunistic infection in patients with HIV and is associated with higher mortality [5]. TB can occur at any stage of HIV infection, from the asymptomatic form to acquired immunodeficiency syndrome (AIDS) [6].

31.3.1 Extrapulmonary Tuberculosis

The main extrapulmonary TB sites are, in descending order: pleural, lymphatic, and urogenital TB. Urogenital TB occurs through hematogenous dissemination and, like other forms of TB, is more frequent in immunosuppressed patients (HIV-positive, transplanted patients, etc.), in which latent *M. tuberculosis* reactivation or primary infections occur [7].

Renal manifestations of TB include proteinuria, hematuria, hypoalbuminemia, and renal dysfunction. The histopathological findings are varied: interstitial inflammatory infiltrate, mesangial proliferation, interstitial granulomas, among others. The association between *M. tuberculosis* infection and interstitial nephritis demonstrates the usually observed chronic course of the infection. The treatment of TB contributes to the reduction in alterations found in the urinary sediment, as well as to renal function improvement.

31.3.2 Renal Impairment in Tuberculosis

Renal impairment in TB may be part of a disseminated infection or be localized in the genitourinary tract [8]. In both cases, the lesions depend basically on the patient's immune status, pathogenicity of the bacillus, and site of infection.

Pulmonary infection is the primary site in most cases. After exposure to the bacillus, the latter remains stored in the macrophages where they slowly multiply. In most cases, the primary infection is self-limiting. The kidneys are commonly affected in cases of miliary TB, where miliary lesions measuring up to 3 mm in diameter are found in renal tissue (mainly cortical) from the hematogenous dissemination [9]. Renal dysfunction may occur in some patients with pulmonary or disseminated TB, with no evidence of typical renal cortical lesions. In these patients, findings of interstitial nephritis (Fig. 31.1) and acid-fast bacilli (AFB) (Fig. 31.2) are common [10].

31.3.3 Pathophysiology of Renal Tuberculosis

Hematogenous dissemination occurs after vascular erosion, usually of a pulmonary vein, with embolism of microorganisms occurring through the systemic circulation.

M. tuberculosis needs favorable environmental conditions for proliferation, which justifies its predilection for certain organs, including the kidney, epididymis, fallopian tube, bone marrow, and brain [9].

In the kidneys, the preferred site for colonization by *M. tuberculosis* is the medullary region, where granulomatous lesions may appear with caseous necrosis and, consequently, tissue destruction. Kidney injury starts in the cortex and, subsequently, the bacillus can migrate to the corticomedullary junction, where granulomas are formed. These remain stable for many years and, in cases of reactivation, the mycobacteria can invade the medulla, causing papillitis, papillary necrosis, and invasion of the collecting system. Dissemination to the renal pelvis can cause tuberculous pyelonephritis and pyonephrosis. The involvement of renal calyces can be unilateral or bilateral, and the findings include diffuse calcifications, destruction, and loss of renal function [8].

Infection can reach the bladder from the ureter, with granulomas associated with areas of fibrosis. In the ureter, the lesions can cause several areas of stenosis, intermingled with areas of

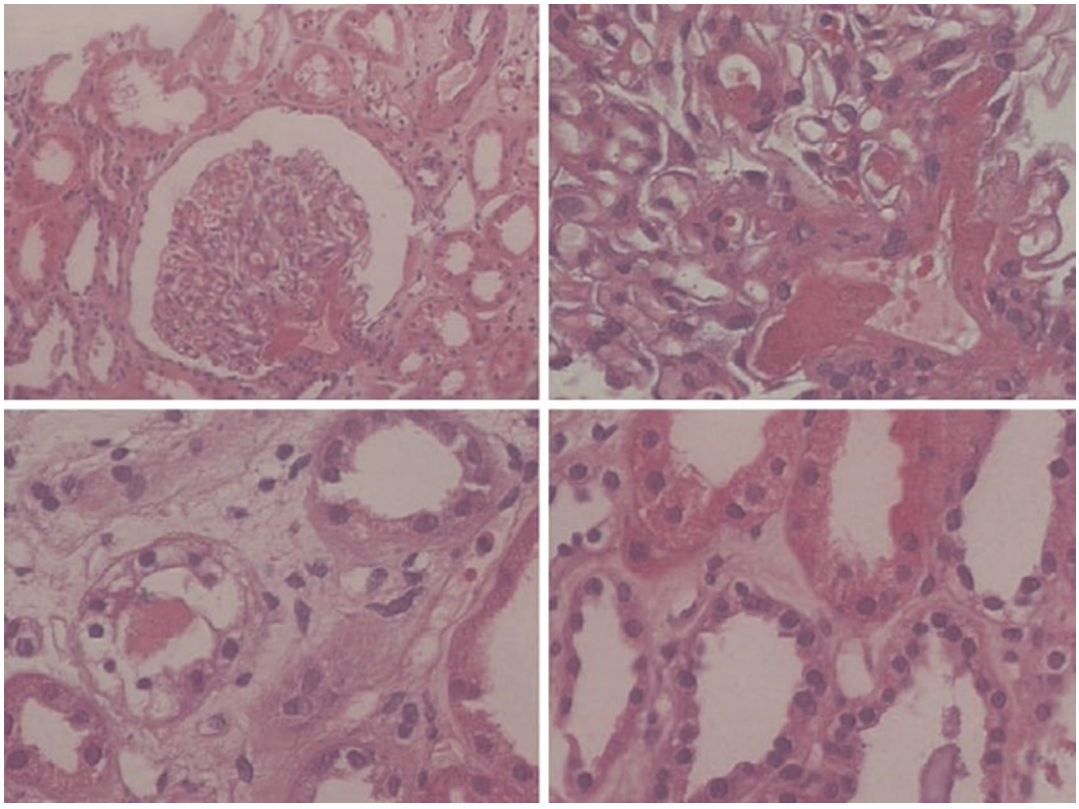


Fig. 31.1 Renal biopsy of a patient with renal TB showing interstitial nephritis. H&E, 400×. (Adapted with permission from Daher et al. [10]. © 2013 The American Society of Tropical Medicine & Hygiene)

dilation, constituting the main finding of urogenital TB in the pyelography. A megaureter can occur in cases of total obstruction or in more distal segments of the ureter (Fig. 31.3) [11, 12]. Another possible presentation of renal TB is the tumoral form, which can mimic neoplastic lesions and result from the dissemination of cortical lesions through the renal capsule.

31.3.4 Clinical Manifestations

It is important that health teams from countries with a high incidence of TB, such as Brazil, are also able to detect cases of extrapulmonary TB and offer the right treatment. The most characteristic pulmonary clinical presentation of TB involves fever, productive cough, night sweats, and weight loss. However, these clinical manifestations are not common in renal TB. After the primary infection, the bacilli can spread, causing lesions to other organs, such as the pleura, lymph nodes, and genitourinary tract [13]. Renal manifestations can include proteinuria, leukocyturia, and loss of renal function. Isolated hematuria may also occur. Low urinary symptoms may occur when the lesions affect the ureters and the bladder. Clinical pictures compatible with urinary tract infection (UTI) accompanied by leukocyturia and negative urinary cultures (sterile leukocyturia) suggest renal TB. Patients with these findings are frequently submitted first to several unsuccessful treatments with antibiotics, and only then renal TB is suspected. It is noteworthy that the vast majority of patients with renal TB are asymptomatic and only 10% of patients have urinary symptoms [14]. All patients diagnosed with renal TB should undergo pulmonary investigation, even though the most frequent findings are scarring only.

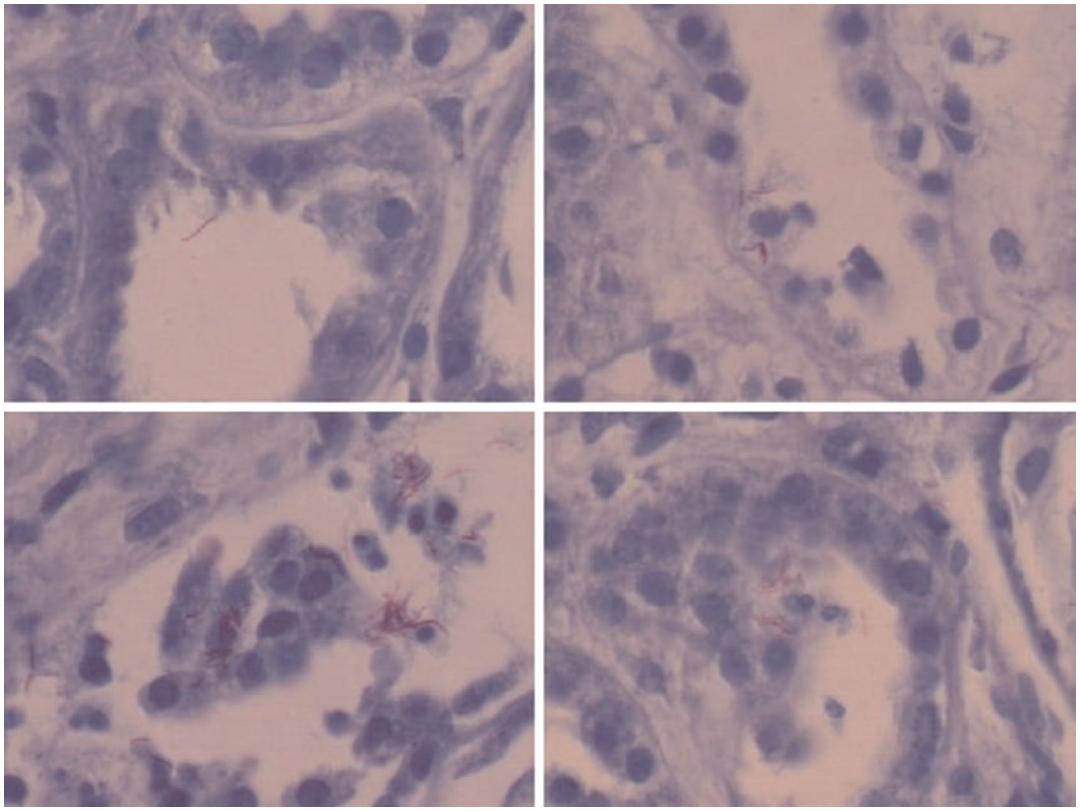


Fig. 31.2 Renal biopsy of a patient with renal TB showing AFB (Ziehl-Neelsen stain). H&E, 400×. TB tuberculosis, AFB acid-fast bacillus. (Adapted with permission from Daher et al. [10]. © 2013 The American Society of Tropical Medicine & Hygiene)

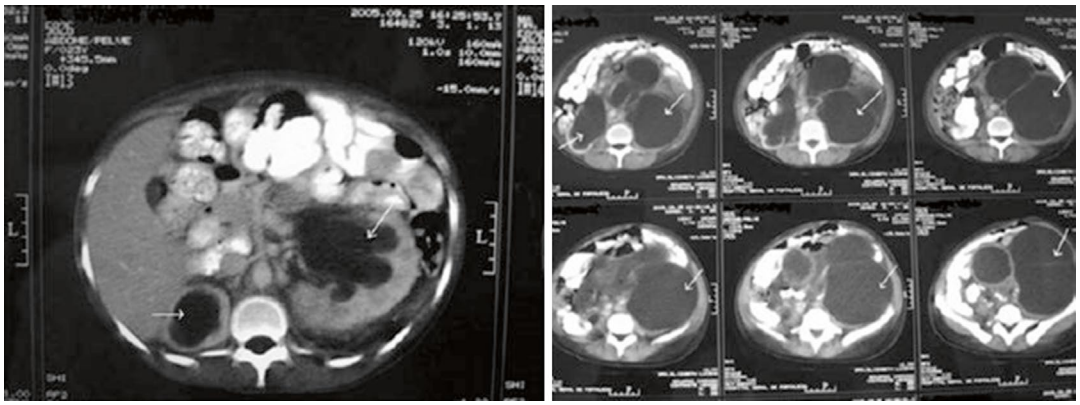


Fig. 31.3 Computed tomography of a patient with renal TB showing enlargement of both kidneys, cortical thinning, markedly dilated calyces, and severe dilation of the ureter (megaureter). (Adapted with permission from Daher et al. [15])

31.3.5 Renal Tuberculosis and Glomerulopathies

Renal TB can cause amyloidosis and is a major cause of chronic kidney disease (CKD) in India [15] and is probably underdiagnosed in other countries. There have been several reports of patients with TB and glomerulonephritis; however, there are no data supporting the cause-and-effect association of TB and these glomerular findings. Our group reported a patient who was diagnosed with lupus nephritis and was later found to have renal TB, based on an AFB-positive urinary culture and renal biopsy showing proliferative glomerulonephritis [16].

31.3.6 Renal Tuberculosis and Chronic Kidney Disease

Despite the availability of effective TB treatment, underdiagnosis still persists in many parts of the world, and that increases the chances of progression to end-stage CKD. Moreover, the underdiagnosis makes it difficult to understand the real effect that TB has on kidney disease progression. The European Renal Association and the European Dialysis and Transplantation Association reported that 0.65% of the patients admitted for dialysis had TB as the primary cause [17]. Among dialysis patients, the risk of TB is up to 50-fold higher than in the general population, and its prevalence ranges between 5% and 25% [18, 19]. Several factors related to dialysis contribute to cell immunity impairment: malnutrition, reduced protein intake, iron overload, dialysis apparatus bioincompatibility, frequent hospital admissions, age, diabetes mellitus, etc. [20].

Our group reported a 32-year-old patient with end-stage CKD, sterile leukocyturia, pleural effusion with high adenosine deaminase (ADA) levels, and a history of pulmonary tuberculosis [21] and a case of a 34-year-old patient with right renal exclusion confirmed by scintigraphy (Fig. 31.4) [22].

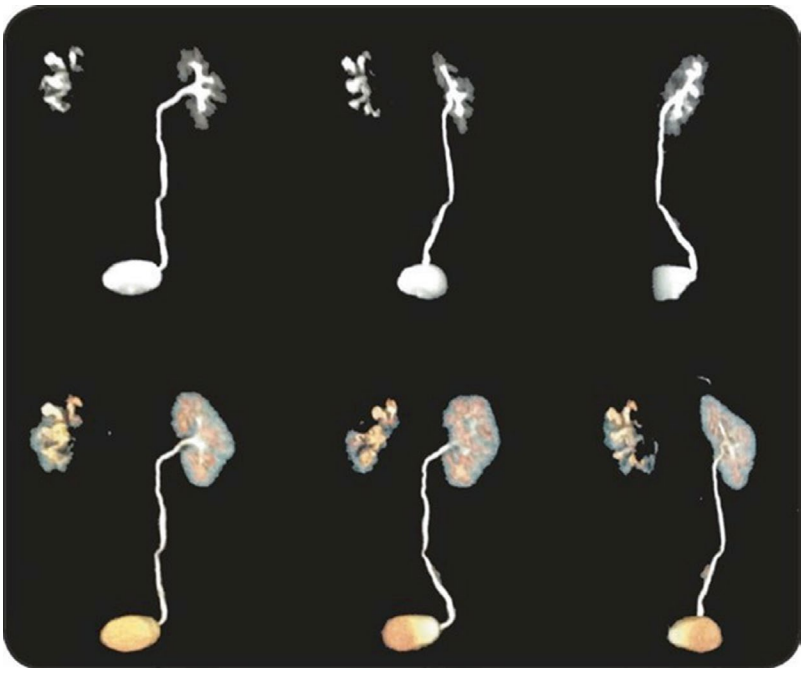


Fig. 31.4 Kidney scintigraphy showing right kidney with reduced size, heterogeneous distribution of the radioisotope and no evidence of excretion. (Adapted with permission from Silva Junior et al. [22])

31.4 Complementary Methods

Advanced renal TB may cause obstructive uropathy, bladder dysfunction, and chronic kidney disease [15]. Imaging methods (ultrasound, computed tomography, and magnetic resonance imaging) may show grossly distorted ureters, alternating areas of stenosis and dilation, as well as reduced volume bladder, pyelocalyceal dilation, and even small-sized kidneys. Pyelography can show loss of renal function, distorted renal calyces, or cavities suggestive of TB [15, 23]. Only a third of patients with renal TB have radiological abnormalities.

31.4.1 Laboratory Assessment

The diagnosis of TB is usually made by isolating the pathogen in a urine or tissue sample. Ziehl-Neelsen staining identifies AFBs in the centrifuged urine sample, but it is important to be aware that false-positive results may occur due to sample contamination by *Mycobacterium spp.*, which are nonpathogenic in the environment [9]. Urinary sediment analysis may range from slight alterations, such as proteinuria and leukocyturia, to extreme pyuria, sometimes accompanied by hematuria. Some findings may suggest renal TB: acid urinary pH, leukocyturia, and/or hematuria, associated with negative urine cultures.

Routine urine cultures are negative. However, cultures with Lowenstein–Jensen medium may be useful for detecting mycobacteria. Several samples (a minimum of three) should be collected to increase the method sensitivity. The time of growth is usually slow, usually 4–8 weeks [11].

More recently, new molecular biology techniques using PCR have been used to obtain faster and more sensitive results for *M. tuberculosis* detection. These techniques also allow evaluating the drug sensitivity profile in cases of suspected resistant pathogen, a frequent problem in endemic areas. In 2013, the GeneXpert MTB/RIF method was implemented in the Brazilian Unified Health System. It is a rapid tool for the diagnosis of TB, as it detects the presence of the genetic material of *Mycobacterium tuberculosis* complex and resistance to rifampicin, with results provided within 2 h [24].

31.5 Treatment

First-line treatment includes rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months, followed by rifampicin and isoniazid for 4 months (Table 31.1) [25]. Second-line drugs are less effective in the treatment and are indicated for patients who cannot tolerate the first-line treatment. The second-line treatment drugs

Table 31.1 Basic TB treatment regimen in Brazil

Regimen	Drugs	Weight	Dose	Months
2 RHZE	RHZE	Up to 20 kg	R: 10 mg/kg/day	2
Intensive phase			H: 10 mg/kg/day	
			Z: 35 mg/kg/day	
			E: 25 mg/kg/day	
		20–35 kg	2 pills	
		36–50 kg	3 pills	
		>50 kg	4 pills	
4 RH	RH	Up to 20 kg	R: 10 mg/kg/day	4
Maintenance phase			H: 10 mg/kg/day	
		20–35 kg	2 pills	
		36–50 kg	3 pills	
		>50 kg	4 pills	

Adapted with permission from Barreto et al. [25]
Dose per pill—*R* rifampicin 150 mg, *H* isoniazid 75 mg, *Z* pyrazinamide 400 mg, *E* ethambutol 275 mg

include capreomycin, ciprofloxacin, clofazimine, cycloserine, ethionamide, kanamycin, levofloxacin, ofloxacin, and aminosalicylic acid.

Resistance to tuberculostatic drugs has been increasing in patients with HIV. Cases of isolated resistance to isoniazid should be treated with rifampicin, pyrazinamide, and ethambutol for 6 months. In cases of suspected resistance to rifampicin, treatment should be carried out with isoniazid and ethambutol for 18 months, or isoniazid, pyrazinamide, and streptomycin for 9 months [26].

Patients with renal impairment can be treated with rifampicin, isoniazid, pyrazinamide, and ethionamide at the usual doses, since these drugs have biliary excretion and are metabolized to other components without significant renal excretion. However, the doses should be adjusted in patients with creatinine clearance ≤30 mL/min or those undergoing dialysis. Avoiding streptomycin and ethambutol is recommended. If there is no other alternative, these drugs should be administered at reduced doses and at longer intervals. The safest scheme is 2HRZ/4HR [27]. If it is impossible to use the basic regimen, other medications are recommended (Table 31.2) [25].

Ethambutol is associated with optic neuritis, which may be reversible if the dose is adjusted according to the glomerular filtration rate (GFR): 25 mg three times a week if GFR is 50–100 mL/min and twice a week if GFR is 30–50 mL/min.

Streptomycin and other aminoglycosides can cause ototoxicity and nephrotoxicity and should be avoided in AKI patients [9]. Encephalopathy is an unusual complication of isoniazid treatment and is usually prevented with the use of pyridoxine (25–50 mg/day). Some patients undergoing hemodialysis have isoniazid-induced encephalopathy that does not improve with pyridoxine, but reversal occurs with drug withdrawal. Since rifampicin interferes with the metabolism of drugs commonly used in immunosuppressive therapy (e.g., corticosteroids, cyclosporine, etc.), serum concentrations should be monitored [9].

The association of corticosteroids with anti-TB treatment can reduce fibrotic alterations. Nevertheless, patients with advanced disease and/or late diagnosis may require surgical interventions [28].

Table 31.2 TB treatment in advanced renal failure

Drug	Dose and frequency
Isoniazid	300 mg/day or 900 mg 3× week
Rifampicin	600 mg/day or 600 mg 3× week
Pyrazinamide	25–35 mg/kg/dose 3× per week
Ethambutol	15–25 mg/kg/dose 3× per week
Ethionamide	250–500 mg/dose daily
Streptomycin	12–15 mg/kg/dose 2–3× per week
Amikacin	12–15 mg/kg/dose 2–3× per week

Adapted with permission from Barreto et al. [25]

31.6 Invasive Procedures

Surgery or other invasive procedures may be performed in the following situations: hydronephrosis drainage (ureteral dilatation or percutaneous nephrostomy), drainage of collections or abscess, definitive treatment of renal TB (partial nephrectomy), upper urinary tract reconstruction, bladder dilation, ureteral reconstruction, and genital TB [26, 29]. In cases of ureteral stenosis, pyelography or ultrasound evaluation should be performed every 6 months for the first 2 years of treatment to detect possible obstructive uropathies and establish timely treatment [11].

31.7 Conclusion

TB has a high incidence in developing countries. Underdiagnosis contributes to the development of multistage kidney failure and even end-stage CKD, which could be prevented with adequate diagnosis and treatment. It is important to emphasize that, due to the large number of patients with HIV or other forms of immunosuppression, physicians should be alert to the suspicion of renal TB in patients with urinary sediment showing unexplained hematuria. Further research is needed to outline the main presentations of renal TB, as well as to develop more effective diagnostic methods and drugs for TB treatment with fewer side effects.

References

1. World Health Organization. Global tuberculosis report 2017. Geneva: World Health Organization; 2017.
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Coordenação-Geral de Desenvolvimento da Epidemiologia em Serviços. Guia de Vigilância em Saúde. 1st ed. Brasília: Ministério da Saúde; 2017.
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico. Brasília: Ministério da Saúde; 2017. p. 48.
4. Rieder HL, Snider DE Jr, Cauthen GM. Extrapulmonary tuberculosis in the United States. Am Rev Respir Dis. 1990;141:347–51.
5. Jamal LF, Moherdaui F. Tuberculose e infecção pelo HIV no Brasil: magnitude do problema e estratégias para o controle. Rev Saude Publica. 2007;41:104–10.
6. Cheade MF, Ivo ML, Siqueira PH, et al. Characterization of tuberculosis among HIV/AIDS patients at a referral center in Mato Grosso do Sul. Rev Soc Bras Med Trop. 2009;42:119–25.
7. Jones BE, Young SM, Antoniskis D, et al. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis. 1993;148:1292–7.
8. Muttarak M, ChiangMai WN, Lojanapiwat B. Tuberculosis of the genitourinary tract: imaging features with pathological correlation. Singap Med J. 2005;46:568–74.
9. Eastwood JB, Corbishley CM, Grange JM. Tuberculosis and the kidney. J Am Soc Nephrol. 2001;12:1307–14.
10. Daher EF, da Silva Jr GB, Barros EJ. Renal tuberculosis in the modern era. Am J Trop Med Hyg. 2013;88:54–64.
11. Yarger WE. Urinary tract obstructive. In: Brenner BM, Rector FC, editors. The kidney. 4th ed. Philadelphia/London: W.B. Saunders; 1991. p. 1768–808.
12. Daher EF, Silva Júnior GB, Pinheiro HC, et al. Erythema induratum of Bazinand renal tuberculosis: report of an association. Rev Inst Med Trop Sao Paulo. 2004;46:295–8.
13. Mandell GL, Bennett JE, Dolin R. In: Mandell GL, Douglas RG, Bennett JE, editors. Principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010.
14. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician. 2005;72:1761–8.
15. Daher EF, Silva Júnior GB, Damasceno RT, et al. End-stage renal disease due to delayed diagnosis of renal tuberculosis: a fatal case report. Braz J Infect Dis. 2007;11:169–71.
16. Silva Júnior GB, Alcântara AC, Marques VB, et al. Lúpus eritematoso sistêmico e Tuberculose renal: relato de caso. Med Interna. 2014;24:157–9.
17. Eastwood JB, Zaidi M, Maxwell JD, et al. Tuberculosis as primary renal diagnosis in end-stage uraemia. J Nephrol. 1994;7:290–3.
18. Ates G, Yildiz T, Danis R, et al. Incidence of tuberculosis disease and latent tuberculosis infection in patients with end stage renal disease in an endemic region. Ren Fail. 2010;32:91–5.
19. Sav T, Tokgoz B, Sipahioglu MH, et al. Extrapulmonary tuberculosis in a hemodialysis patient with unusual clinical presentation. Int Urol Nephrol. 2010;42:223–6.
20. Christopoulos AI, Diamantopoulos AA, Dimopoulos PA, et al. Risk factors for tuberculosis in dialysis patients: a prospective multi-center clinical trial. BMC Nephrol. 2009;10:36.
21. Lima NA, Vasconcelos CC, Filgueira PH, et al. Review of genitourinary tuberculosis with focus on end-stage renal disease. Rev Inst Med Trop Sao Paulo. 2012;54:57–60.
22. Silva Junior GB, Brito Luiz DS, Rabelo ST, et al. Chronic kidney disease related to renal tuberculosis: a case report. Rev Soc Bras Med Trop. 2016;49:386–8.
23. Oliveira JL, Silva Junior GB, Daher EF. Tuberculosis-associated chronic kidney disease. Am J Trop Med Hyg. 2011;84:843–4.
24. Lima TM, Belotti NC, Nardi SM, et al. Teste rápido molecular GeneXpert MTB/RIF para diagnóstico da tuberculose. Rev Panamazonica Saude. 2017;8:65–76.
25. Conde MC, Fiuza de Melo FA, Marques AM, et al. III Diretrizes para Tuberculose da Sociedade Brasileira de Pneumologia e Tisiologia. J Bras Pneumol. 2009;35:1018–48.
26. Hanno P. Genitourinary tuberculosis. AUA News. 2001;6:10.
27. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of anti-tuberculosis therapy. Am J Respir Crit Care Med. 2006;174:935–52.
28. Wise GJ, Marella VK. Genitourinary manifestations oftuberculosis. Urol Clin North Am. 2003;30:111–21.
29. Small PM, Fujiwara PI. Management of tuberculosis in the United States. N Engl J Med. 2001;345:189–200.

32 Syphilitic Nephropathy

Romélia Pinheiro Gonçalves Lemes, Suzzy Maria Carvalho Dantas, Igor Ribeiro de Lemos, João Filipe Cavalcante Uchoa Furtado, Pedro Vianna Caldas Ribeiro, Elizabeth De Francesco Daher, and Geraldo Bezerra da Silva Junior

32.1 Introduction

Syphilis is an infectious disease caused by the spirochete bacterium *Treponema pallidum*. It is transmitted through unprotected sexual contact with infected people or via the transplacental route during pregnancy or childbirth [1, 2]. The disease has well-defined stages and established treatments, but its diagnosis can be challenging due to the various clinical manifestations, which can affect a single organ or manifest in a multisystemic way [3, 4, 5, 6], which is why it is often called the "great imitator" [3, 4, 7].

In recent years, there has been an increase in cases of syphilis, including atypical manifestations, which have been reported in various parts of the world. Many of these cases are aggravated and disguised by co-infections, which can lead to neglect of the real cause complicating diagnosis and proper treatment.

R. P. G. Lemes · S. M. C. Dantas
Pharmaceutical Sciences Graduate Program, Federal University of Ceara, Fortaleza, Ceara, Brazil

I. R. de Lemos · E. De Francesco Daher
Department of Internal Medicine, School of Medicine, Federal University of Ceara, Fortaleza, Ceara, Brazil

J. F. C. U. Furtado · P. V. C. Ribeiro
G. Bezerra da Silva Junior (✉)
School of Medicine, University of Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

32.2 Epidemiology

In 2022, according to an annual epidemiological report by the European Center for Disease Prevention and Control (ECDC), a total of 35.391 cases of syphilis were reported in 29 member countries of the European Union and European Economic Area with an incidence rate of 8.5 cases/100.000 inhabitants [10].

In the United States, since the historic low in 2000 and 2001, the rate of syphilis has risen every year, with the overall rate of primary and secondary syphilis cases increasing around five times. A report by the Centers for Disease Control and Prevention (CDC) states that in 2022, 207.255 cases of acquired syphilis were reported in the country [11].

In Brazil, 213.129 cases of acquired syphilis were reported in 2022, a rate of 99.2 cases/100,000 inhabitants. The high number of cases has compelled government initiatives to develop education, prevention, diagnosis, and treatment strategies. Despite protocols for prenatal care, 26.468 cases of congenital syphilis were reported in Brazil in 2022, with a mortality rate of 7.8/100.000 live births [12].

With the introduction of penicillin for the treatment of syphilis in 1943, and with advances in epidemiological surveillance, worldwide cases of syphilis have fallen considerably and, in some countries, the WHO has considered vertical transmission of this infection to have been

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_32

eradicated [13]. However, cases of syphilis have been on the rise worldwide in recent years, making it a major public health problem [10, 11, 12].

32.3 Stages of Syphilis

The stages of syphilis are related to its clinical manifestations and time of infection, and are classified as primary, secondary, latent, and tertiary syphilis, which can be early or late [14].

Early syphilis comprises the primary, secondary, and early latent stages which occur less than 2 years after acquiring the infection. Late syphilis refers to the late latent and tertiary stages.

The World Health Organization (WHO) classifies syphilis as primary with the presentation of an ulcer at the site of infection, which develops in an incubation period of around 3 weeks after sexual contact. If left untreated, the ulcer disappears without scarring after around 2-10 weeks and then progresses to the secondary stage. In the secondary stage, which appears 6 weeks to 6 months after infection, the spirochetes enter the bloodstream and can cause systemic symptoms such as fever, malaise, arthralgia, and anorexia. If left untreated at this stage, syphilis goes into latency or progresses to the tertiary stage, which appears between 1 and 40 years after the start of infection and usually presents skin, bone, cardiovascular, and neurological lesions, and can lead to death.

32.4 Mechanisms of Kidney Injury in Syphilis

Kidney disease due to syphilis is uncommon, but it is seen in 0.3% of secondary syphilis cases [15], although there are reports of it occurring in tertiary syphilis [16], congenital syphilis [17], and even subclinical syphilis [18, 19]. In the second stage of syphilis, *Treponema pallidum* spreads through the bloodstream and reaches various organs in the body, causing skin rashes, generalized condylomas, and joint and eye lesions. Nephropathy also develops at this stage [7].

The most common kidney lesion in syphilis is glomerulopathy, especially membranous glomerulonephritis, manifesting with proteinuria [7, 8]. Few studies report spontaneous remission of proteinuria caused by syphilitic membranous glomerulonephritis [20],

more common is rapid improvement in kidney function after adequate antibiotic therapy [7, 21, 23, 24, 25, 26, 28]. Immunosuppressants, commonly used in the treatment of idiopathic membranous glomerulonephritis, could result in progression of the syphilis stage by suppressing the immune system [26, 28].

32.5 Membranous Glomerulonephritis

Membranous glomerulonephritis is one of the main causes of nephrotic syndrome and affects a wide age range, from 18 to 71 years [29]. This syndrome can have primary or secondary causes, with only 25% of secondary causes, syphilis being listed as one of them. Patients usually present with acute onset nephrotic syndrome, and less frequently, other symptoms such as maculopapular rash, mucocutaneous lesions, hepatitis, and lymphadenopathy [29], with the main clinical manifestations of nephrotic syndrome being edema, hypoalbuminemia, hypertension, dyslipidemia, and proteinuria of 3.0–3.5g in 24 h [30, 31], which can occur with nephropathy in addition to other clinical manifestations, such as ocular alterations [32], leukocytoclastic vasculitis [33], gastric syphilis [20, 21], intestinal syphilis [34], and arthralgia [31].

Because of the range of symptoms that can be associated with the disease, it is very important to consider syphilis in the differential diagnosis of membranous nephropathy, as syphilis can also cause false-positive elevation of antinuclear antibodies (ANA) [29] titers and further confuse the diagnosis, leading to errors in treatment, for example, with the use of immunosuppressants.

Pathological examination of kidney tissue showed the presence of treponemal antigens and antibodies against *Treponema pallidum*, with renal biopsy showing glomerular deposits of IgG, C3

protein from the complement system, an increase in the mesangial matrix, with thickening of the capillary loops, and the presence of inflammatory cells. Electron microscopy commonly shows subepithelial deposits [5, 7, 8]. This provides evidence of the role of immune complex-mediated lesions in syphilis. The production of immune complexes with complement activation can cause glomerulonephritis, but can also contribute to the vascular inflammation seen in syphilitic kidneys [29]. Although these findings are common, glomerulonephritis can occur without evidence of structural alterations under light microscopy, but with granular depositions of immunoglobulins under immunofluorescence microscopy, characterizing early-stage glomerulonephritis [37, 40].

32.6 Other Kidney Abnormalities in Syphilis

In addition to membranous glomerulonephritis, a case of segmental and focal glomerulosclerosis (FSGS) has also been reported as a cause of nephrotic syndrome in a patient with late latent syphilis, showing IgM deposition in mesangial regions and in segmental lesions, with other causes of secondary glomerulosclerosis being excluded and renal function normalizing after antibiotic therapy [3, 29].

Other glomerular alterations have already been described in the renal manifestation of syphilis, such as segmental-focal glomerulosclerosis [3] (FSGS), minimal change glomerulopathy [42], rapidly progressive glomerulonephritis [43], and post-infectious glomerulonephritis with a predominance of IgA deposits [44].

Few syphilitic nephropathies not directly involved to the glomerulus, such as tubulointerstitial nephritis, have been reported [45, 46] (Table 32.1).

In the case of tubulointerstitial nephritis, there may be an increase in urinary sodium, hyponatremia, without the occurrence of proteinuria, since it can occur without glomerular involvement [8, 45]. However, there may also be mixed involvement, as in the case report by Noutong et al. [8], in which in addition to glomerular alterations, mild chronic kidney damage was also found, with 15% tubular atrophy and signs of interstitial fibrosis. In the case report by Qi et al. [47], rapidly progressive glomerulonephritis concomitant with acute tubulointerstitial nephritis was reported in a patient with syphilis.

Kidney involvement may have an indirect cause, as is the case of acute kidney injury (AKI) associated with rhabdomyolysis in syphilis [48, 49] and the presence of a renal mass [16].

Table 32.1 Summary of syphilitic renal changes reported in the literature

Location of change	Change specification	References
Glomerular changes	Membranous glomerulonephritis	[24]
	Segmental glomerulosclerosis	[41]
	Rapidly progressiveglomerulonephritis	[43]
	Minimum change glomerulopathy	[42]
	Glomerulopathy post-infectious withpredomínio de depósitos de IgA	[44]
Tubulointerstitial changes	Interstitial nephritis	[45, 46]
Mixed changes	Glomerulonephritis and tubular atrophy	[8]
	Rapidly progressive	[43]
	Glomerulonephritis and acute tubulo intertitial nephritiskindey mass	
Others	Acute kidney injury and rhabdomyolysis	[48, 49]

32.7 Kidney Abnormalities in Congenital Syphilis

Kidney involvement has also been better evaluated in congenital syphilis since the middle of the twentieth century, with reports dating back to 1939 [50]. The incidence rate of renal syphilis in the context of congenital syphilis ranges from 0.5% to 2.4%. This is thought to result from direct invasion of the kidneys by spirochetes or secondary to a hypersensitivity reaction [26].

Nephrotic syndrome has been described in congenital syphilis, some with histological analysis, with common findings of basement membrane thickening due to igG deposition [50, 51], similar to the findings in secondary syphilis glomerulonephritis. This syndrome, when congenital, presents from 0 to 3 months of life and can be caused by, in addition to congenital syphilis , toxoplasmosis, viral infections or genetic defects in the structural proteins that form the glomerular filtration barrier [52, 53].

Kidney involvement varies from mild albuminuria to severe disease, but regression is rapid when treatment is carried out properly, which evidence a transient immunological disease. This understanding is reinforced by the fact that signs of congenital syphilis nephropathy appear 6–8 weeks after birth, which raises the hypothesis that treponema should not be the main cause of kidney damage, but rather the immune response with the formation of immune complexes [54].

In a cohort study by Garcia et al. [17], 4 newborns (6.5%) out of 61 with congenital syphilis followed up had persistent kidney disorders, presenting with nephrotic syndrome, two of which expressed massive proteinuria, and the other two with mild proteinuria and hematuria, highlighting the importance of adequate maternal and infant serological analysis for early diagnosis and treatment.

32.8 Kidney Changes in Syphilis: Co-infections

Kidney manifestations of patients with syphilis who are co-infected with viral hepatitis and/or HIV should be carefully evaluated, since both infections can generally cause nephropathy [5].

Syphilis, known as the "great imitator," has a range of clinical manifestations, including syphilitic hepatitis and syphilitic nephropathy, which usually only regress with adequate antibiotic therapy [9]. Hepatitis B, Hepatitis C, or HIV-positive patients with *T. pallidum* co-infection may have their nephropathy wrongly attributed to viral hepatitis or HIV itself. In these cases, it is necessary to investigate the patient's general condition and analyze co-infections in order to explain the correct cause of the clinical manifestations and the appropriate treatment [5, 25, 41, 43].

The practice of sex without a condom has become even more problematic due to the introduction of pre-exposure prophylaxis (PrEP) and the adoption of "serosorting" behavior (choosing sexual partners based on HIV serological status). In addition, the growing use of the Internet to find sexual partners has been linked to an increase in high-risk sexual activities, such as having multiple partners and the use of substances during sexual relations [56, 57, 58, 59].

The most commonly reported syphilitic nephropathy associated with HIV co-infection is membranous glomerulonephritis [5]. Cases of glomerulosclerosis [41], tubulointerstitial alterations with fibrosis and mononuclear cell infiltrate [41], and stage 3 acute kidney injury (AKI) due to tubular necrosis [60] have also been reported.

Although syphilitic nephropathy, in the absence of co-infections, is rarely associated with hepatic manifestations [35, 36, 61], in the study by Chun-Chi Yang (2024) [66], a case of second-

ary syphilis presenting simultaneously with syphilitic hepatitis and syphilitic nephrotic syndrome is reported after evaluation of the clinical picture, the patient's sexual history, syphilis serological markers, urine analyses, and renal biopsy results, as a result of which he received three doses of penicillin G benzathine (2.4 million units) once a week, plus valsartan and pentoxifylline, which were prescribed for hypertension and proteinuria due to their proteinuria-reducing effects. Follow-up after 4 weeks showed favorable responses to treatment. Another study by Luwawwu et al. (2014) [39] reports a case of nephrotic syndrome and hepatic hilar lymphadenopathy in a patient with syphilis.

On the other hand, this association seems to be increased in HIV patients co-infected with syphilis, with reports of simultaneous nephropathies and liver alterations, ranging from transient alterations in transaminases and alkaline phosphatase [62, 66], to more significant cases such as hepatosplenomegaly [6, 66], hepatitis [9], intrahepatic mass [63], hepatic granuloma [6], all caused by syphilis. It is possible that the immunological impairment of these patients leads to greater systemic expression of treponema pallidum, presenting more aggressive atypical manifestations and a rapid clinical course [9], but this hepatorenal association in syphilis needs further investigation.

Although syphilis co-infections with HIV and/or viral hepatitis are more common because they share the mode of transmission [9], other types of co-infections with syphilitic renal manifestations can also occur, such as the study by Jaunin et al. (2019) [64], which presents a case of syphilis and parvovirus B19 co-infection mimicking lupus nephritis. Although this nephritis can be distinguished from syphilitic glomerulonephritis by assessing other markers such as antinuclear factor (ANF), in the case reported there was both the deposition of standard "full house" immunoglobulins and marking for ANF due to the presence of parvovirus B19, a finding similar to that of lupus nephritis and unexpected for syphilitic nephritis, with only the "full house" pattern being more common [67, 68], highlighting the importance of assessing co-infections for proper diagnosis and treatment.

32.9 Immunohistopathological Findings in Syphilitic Kidney Manifestations

Although IgG and C3 labeling for glomerular deposits stands out in immunofluorescence analysis of kidney biopsies from syphilitic nephropathies [5, 8, 29, 61], occasionally the panel of markings can be broad, with IgA, IgM, C1q complement fractions, as well as kappa and lambda light chains known as the "full house" pattern [9, 29, 65], similar to the findings in lupus nephritis [29, 64]. In a study by Wanderley et al. (2021) [65], three out of ten syphilis patients evaluated with membranous nephropathy showed a "full house" pattern in immunofluorescence findings.

In a study by Guillén et al. (2019) [44], a case of acute glomerulonephritis with a predominance of IgA deposits was reported in a pregnant woman with syphilis. This emerging nephropathy, unlike the renal disorders that have been associated with syphilis, is characterized by subepithelial IgA deposits without mesangial involvement, with a variable clinical course generally encompassing an acute nephrotic phase. The disease has been associated with staphylococcal infections, as well as infections by *Escherichia coli*, Enterococcus *sp.* and other pathogens; however, no case had ever been associated with *T. pallidum* infection.

In a study by Zhou et al. [46], a 56-year-old patient presented with polyuria and polydipsia,

with a water deprivation test indicating nephrogenic diabetes insipidus (NDI). NID is characterized by resistance of the renal collecting tubules to the action of endogenous or exogenous antidiuretic hormone endogenous or exogenous. The kidney biopsy showed no glomerular alterations, but it did show small, flat tubular epithelial cells, indicating tubular damage. Silver staining revealed the presence of *T. pallidum* organisms in the kidneys, and immunofluorescence (IF) showed a specific antibody to *T. pallidum*. Penicillin therapy was carried out, with improvement in polyuria and polydipsia after a month.

In tertiary syphilis, in a report by Carvalho [16], a patient presented with an unusual case of a renal mass. Histological analysis showed extensive coagulative necrosis, with chronic granulomatous inflammation and deep infiltration of mononuclear cells, with the presence of glomerular sclerosis in adjacent areas and significant regression of the renal mass after antibiotic therapy.

In addition, also in tertiary syphilis, *T. pallidum* can invade the aortic wall and weaken the tunica, forming aneurysms and associated aortic valve insufficiency, which can lead to the formation of thrombi and subsequent embolism of the renal tissue, resulting in renal infarcts, as reported by Spaltenstein [69], where the patient had acute kidney injury, and computed tomography (CT) showed a right renal infarct with intraluminal thrombus and after treatment with anticoagulation and penicillin the condition resolved.

32.10 Importance of Differential Diagnosis of Syphilis in the Investigation of Kidney Changes of Unknown Cause

Due to the wide range of clinical manifestations, syphilis has been called “the great imitator” [9]. Several case reports demonstrate how screening for syphilis is crucial for proper treatment and symptom remission.

In a study by Gooskens et al. [34], a patient with ulcerations on the intestinal mucosa was treated with mesalamine suppository therapy for clinically presumed ulcerative colitis. During 4 weeks of therapy, the patient developed ankle edema, maculopapular eruptions, and nephrotic syndrome due to membranous glomerulopathy. Subsequently, serology for syphilis was confirmed and immunofluorescence analysis of intestinal sections confirmed the presence of *T. pallidum* spirochetes, confirming syphilis' great ability to mimic other diseases.

In a case study by Kaynar et al. [27], there was, until then, the first case report of nephrotic syndrome due to primary membranous glomerulopathy in a patient with latent syphilis. The patient was treated with benzathine penicillin without regression of proteinuria, then treated with steroids and cyclosporine, with regression of proteinuria within a month. The search for anti-phospholipase A2 receptor antibody (Anti-PLA2Rab) and the lack of remission of proteinuria with treatment for syphilis was fundamental for the diagnosis of primary membranous glomerulopathy. The author emphasizes that if treatment for syphilis had not been carried out, treatment with immunosuppressants could have led to progression of the infection.

In a study by Obimah et al. [70], a patient was admitted with signs of cholestatic liver damage, dilated bile ducts, and anti-mitochondria antibody, characteristics consistent with the diagnosis of primary biliary cholangitis (PBC). However, as well as having proteinuria, choluria, and a protein/creatinine ratio of 6667 mg/g, the patient also had a skin rash on her palms, soles, trunk, face, and groin. After an RPR (rapid plasma reagin) test, titration was 1:128, confirming the diagnosis of secondary syphilis, she was treated with penicillin and her symptoms improved after a month.

In 2016, an unusual case of rhabdomyolysis was reported by Nelson et al. [49]. A patient with anuria due to kidney damage secondary to rhabdomyolysis was diagnosed with secondary syphilis. Hemodialysis was performed, showing little change in creatinine phosphokinase levels. Only after antibiotic therapy was there a rapid improvement in the rhabdomyolysis and complete resolution of the kidney damage.

32.11 Conclusion

Syphilis is a reemerging disease and a global health problem. Although it has been considered eradicated in some countries, the increase in cases has caused concern mainly due to its multisystemic action and because it is associated with other infections, presenting several manifestations and making its diagnosis difficult. Renal alterations in syphilis, although not the main manifestation, are characterized mostly by deposition of immune complexes at the glomerular level. Tubulointerstitial alterations have also been reported, demonstrating the mimetic capacity of this disease when compared to renal manifestations secondary to other infections. Screening for syphilis is crucial for the adequate treatment of renal manifestations, reducing the harm to health, in addition to contributing to the reduction of its transmission.

References

1. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. N Engl J Med. 2020;382(9):845–54. ISSN 1533-4406. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32101666
2. Peeling RW, Mabey D, Chen XS, Garcia PJ. Syphilis. Lancet. 2023;402(10398):336–46. https://doi.org/10.1016/S0140-6736(22)02348-0. PMID: 37481272. https://pubmed.ncbi.nlm.nih.gov/37481272/
3. Hartley AJ, et al. Syphilis masquerading as focal segmental glomerulosclerosis. Int J STD AIDS. 2014;25(7):529–31. ISSN 1758-1052. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24535692
4. Mattei PL, et al. Syphilis: a reemerging infection. Am Fam Physician. 2012;86(5):433–40. ISSN 1532-0650. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22963062
5. Inayat F, et al. Membranous glomerulonephritis as an uncommon presentation of secondary syphilis: a reminder on therapeutic decision-making in clinical practice. J Investig Med High Impact Case Rep. 2020;8:2324709620967212. ISSN 2324-7096. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33078640
6. Kasper P, et al. Cholestatic hepatitis with concomitant nephrotic syndrome due to late syphilis in an immunocompetent 32-year-old man. BMJ Case Rep. 2020;13(2):5. ISSN 1757-790X. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32029514
7. Kaiga A, Sato Y, Arakawa H, et al. Crescentic glomerulonephritis associated with syphilis: a case report and review of the literature. J Med Case Reports. 2023;17:549. https://doi.org/10.1186/s13256-023-04293-2.
8. Noutong SA, et al. A red herring in the green grass: syphilitic membranous glomerulonephritis. Am J Med. 2017;130(3):285–7. ISSN 1555-7162. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27888054
9. Zhang Z, et al. Secondary syphilis associated with membranous nephropathy and acute hepatitis in a patient with HIV: A Case Report. Perm J. 2018;22:17–062. ISSN 1552-5775. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29236656
10. European Centre for Disease Prevention and Control. Syphilis. In: ECDC. Annual Epidemiological Report for 2022. Stockholm: ECDC; 2024.
11. National Academies of Sciences, Engineering, and Medicine. Sexually Transmitted Infections: Adopting a Sexual Health Paradigm. Washington, DC: The National Academies Press; 2021. https://doi.org/10.17226/25955
12. Brasil. Boletim Epidemiológico. Sífilis/2023. Brasília (DF): Ministério da Saúde; 2023.
13. Organizaçao Pan-Americana da Saúde. [Internet]. Organização Mundial da Saúde publica novas estimativas sobre sífilis congênita, 2019 [access 28 out 2021]. Available from: https://www.paho.org/pt/noticias/28-2-2019-organizacao-mundial-da-saude-publica-novas-estimativas-sobre-sifilis-congenita
14. Guidelines for the management of symptomatic sexually transmitted infections. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
15. Hunte W, Al-Ghraoui F, Cohen RJ. Secondary syphilis and the nephrotic syndrome. J Am Soc Nephrol. 1993;3:1351–5. https://doi.org/10.1681/ASN.V371351.
16. De Carvalho JG, Slongo EL, Sobral AC. Kidney mass and osteolytic lesion: is it always malignancy? Nephrol Dial Transplant. 2007;22(2):645–8. ISSN 0931-0509. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17121783
17. Garcia LN, et al. Congenital syphilis in Argentina: experience in a pediatric hospital. PLoS Negl Trop Dis. 2021;15(1):e0009010. ISSN 1935-2735. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33406082
18. Soehardy Z, et al. Subclinical acquired syphilis masquerading as membranous glomerulonephritis. Med J Malaysia. 2006;61(4):484–6. ISSN 0300-5283. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17243528
19. Wikonkál N, et al. Syphilitic glomerulonephritis: case report and review of the literature. Orv Hetil. 2015;156(1):32–5. ISSN 0030-6002. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25544053
20. Roh M, et al. Gastric Syphilis and Membranous Glomerulonephritis. Clin Endosc. 2015;48(3):256–9.

ISSN 2234-2400. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26064828
21. Fernandes AR, et al. Self-limited membranous glomerulonephritis due to syphilis. J Eur Acad Dermatol Venereol. 2017;31(11):e501–2. ISSN 1468-3083. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28500723
22. Tognetti L, et al. Unusual presentation of secondary syphilis: membranoproliferative glomerulonephritis andmuco-cutaneous lesions. Int J STD AIDS. 2018;29(4):410–3. ISSN 1758-1052. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28950764
23. Araújo SEA, et al. Membranous glomerulonephritis secondary to syphilis. Braz J Infect Dis. 2015;19(4):442–3. ISSN 1678-4391. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25997782
24. Satoskar AA, et al. An uncommon cause of membranous glomerulonephritis. Am J Kidney Dis. 2010;55(2):386–90. ISSN 1523-6838. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19643521
25. Handoko ML, et al. Syphilis: a reversible cause of nephrotic syndrome. BMJ Case Rep. 2013;8. Feb 08 2013. ISSN 1757-790X. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23396933
26. Kim YH, et al. Congenital syphilis presenting with only nephrotic syndrome: reemergence of a forgotten disease. J Korean Med Sci. 2017;32(8):1374–6. ISSN 1598-6357. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28665076
27. Erlij D, Sepúlveda P. Kidney disease in secondary syphilis: a case report. Enfermedades infecciosas y microbiologia clinica (English ed.); 2020. 11/06/2020. ISSN 2529-993X. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33168357
28. Kaynar K, et al. Don't forget syphilis in membranous nephropathy before immunosuppressants: Latent syphilis in a patient with proteinuria. Nefrologia (Engl Ed). 2020;40(6):681–2. Nov–Dec 2020. ISSN 2013-2514. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32144011
29. Shettigar R, Schollum J, Putt T, Chan L, Lau M, Walker R. Renal manifestations of syphilis. Internal Medicine Journal. 2021;51(7):1160–7. https://doi.org/10.1111/imj.15407.
30. Politano SA, Colbert GB, Hamiduzzaman N. Nephrotic syndrome. Primary care. 2020;47(4):2020. ISSN 1558-299X. Available from: https://pubmed-ncbi-nlm-nih.ez11.periodicos.capes.gov.br/33121631/
31. Anton Pampols P, Espejo-Herrera N, Coloma A. Membranous nephropathy related to secondary syphilis. Med Clin (Barc). 2021;157(12):596–7. ISSN 1578-8989. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33858673
32. Bellomo G, et al. A 34-year-old man with membranous nephropathy, a rash, meningitis and ocular involvement. NDT Plus. 2008;1(5):346–8. ISSN 1753-0784. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25983931
33. Cam H, et al. Congenital syphilis presenting with nephrotic syndrome and leucocytoclastic vasculitis. J Eur Acad Dermatol Venereol. 2004;18(4):484–6. ISSN 0926-9959. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15196169
34. Gooskens J, et al. Clinical challenges and images in GI. Syphilitic sigmoiditis complicated by membranous nephropathy. Gastroenterology. 2008;135(2):363–716. ISSN 1528-0012. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18619452
35. Tatu AL, et al. A rare case of syphilis associated with renal and hepatic involvement. Dermatol Pract Concept. 2013;3(4):53–4. ISSN 2160-9381. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24282667
36. Ishiwatari A, et al. Simultaneous nephrotic syndrome and hepatitis in secondary syphilis: case report and review of the literature. CEN Case Rep. 2015;4(2):223–7. ISSN 2192-4449. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28509108
37. Van Herwerden MC, et al. Nephrotic syndrome and a maculopapular rash. Am J Kidney Dis. 2019;73(4):A13–6. ISSN 1523-6838. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30905362
38. Koenig M, et al. Rash and nephrotic syndrome: consider syphilis. Presse Med. 2005;34(9):657. ISSN 0755-4982. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15988342
39. Luwawu M, et al. Abdominal pain, weight loss and asthenia in a 42-year-old man. Rev Med Interne. 2014;35(7):480–2. ISSN 1768-3122. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24856359
40. Chan LW, et al. Nephrotic syndrome related to luetic disease. Kidney Int. 2020;97(5):1062. ISSN 1523-1755. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32331585
41. Bani-Hani S, et al. Renal disease in AIDS: it is not always HIVAN. Clinical and Experimental Nephrology. 2010;14(3):263–7. ISSN 1437-7799. Available from: https://link.springer.com/article/10.1007%2Fs10157-009-0253-8
42. Stubanus M, et al. Quiz page. Minimal change glomerulonephritis associated with secondary syphilis. Am J Kidney Dis. 2007;49(6):A49–50. ISSN 1523-6838. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17687805
43. Siddiqui RS, Sumbly V, Abrudescu A. A case of rapidly proliferative glomerulonephritis secondary to syphilis that responded to treatment with penicillin. Cureus. 2021;13(2):e13468. ISSN 2168-8184. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33777557
44. Orozco Guillén AO, et al. Acute IgA-dominant glomerulonephritis associated with syphilis infection in a pregnant teenager: a new disease association. J Clin Med. 2019;8(1) ISSN 2077-0383. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30669309

45. Chen YC, et al. Salt loss and hyponatraemia in a patient with syphilitic nephritis. Nephrol Dial Transplant. 2005;20(6):1248–50. ISSN 0931-0509. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15855196
46. Zhou J, et al. Nephrogenic diabetes insipidus secondary to syphilis infection. J Clin Endocrinol Metab. 2013;98(7):2663–6. ISSN 1945-7197. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23609837
47. Qi A, Fiset PO, Pilozzi-Edmonds L. Syphilis-related rapidly progressive glomerulonephritis: a case presentation. BMC nephrology. 2021;22(1) ISSN 1471-2369. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34034668
48. Estévez RF. Neurosyphilis presenting as rhabdomyolysis and acute renal failure with subsequent irreversible psychosis and dementia. Psychosomatics. 2006;47(6):538–9. Nov–Dec 2006. ISSN 0033-3182. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17116961
49. Nelson TV, Blaceri S, Biederman JI. Rhabdomyolysis and acute renal failure with syphilitic myositis. Kidney Int. 2016;89(5):1169. ISSN 1523-1755. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27083298
50. BS K, et al. The glomerulopathy of congenital syphilis—an immune deposit disease. The Journal of pediatrics. 1972;81(6) ISSN 0022-3476. Available from: https://pubmed-ncbi-nlm-nih.ez11.periodicos.capes.gov.br/4566039/
51. Suskind R, Winkelstein JA, Spear GA. Nephrotic syndrome in congenital syphilis. Arch Dis Child. 1973;48(3):237–9. ISSN 1468-2044. Available from: https://www.ncbi.nlm.nih.gov/pubmed/4120917
52. Wang JJ, Mao JH. The etiology of congenital nephrotic syndrome: current status and challenges. World J Pediatr. 2016;12(2):149–58. ISSN 1867-0687. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26961288
53. Downie ML, et al. Nephrotic syndrome in infants and children: pathophysiology and management. Paediatr Int Child Health. 2017;37(4):248–58. ISSN 2046-9055. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28914167
54. Norero VC, Flores SM, Schilling IE, Gutiérrez LR. Compromiso Renal en la Lues Congénita [Renal Compromise in the Congenital Lues]. Rev chil pediatr. 1984;55(1):34–7. https://doi.org/10.4067/S0370-41061984000100007.
55. Zhao T, Chen G, Sun C, Gong X, Li H, Fu G. The epidemic of HIV and syphilis and the correlation with substance abuse among men who have sex with men in China: a systematic review and meta-analysis. Front Public Health. 2023;11:1082637. https://doi.org/10.3389/fpubh.2023.1082637. PMID: 36875380; PMCID: PMC9982104
56. Volk JE, et al. No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. Clinic Infect Dis. 2015;61(10):1601–3. https://doi.org/10.1093/cid/civ778. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
57. La Fata L, et al. High asymptomatic STI prevalence and incidence in French MSM starting PrEP. San Diego: IDWeek; 2017. p. 2017.
58. Lal L, et al. Medication adherence, condom use and sexually transmitted infections in Australian preexposure prophylaxis users. AIDS. 2017;31(12):1709–14. https://doi.org/10.1097/qad.0000000000001519. [PubMed] [CrossRef] [Google Scholar]
59. Scott HM, Klausner JD. Sexually transmitted infections and pre-exposure prophylaxis: challenges and opportunities among men who have sex with men in the US. AIDS Research and Therapy. 2016;13(1) https://doi.org/10.1186/s12981-016-0089-8. [PMC free article] [PubMed]
60. Cook H, Gompels M. The wrong Spirochaete? Acute kidney injury in a returning traveller with syphilis—a case report. BMC Infect Dis. 2020;20(1):692. ISSN 1471-2334. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32957955
61. Canney M, et al. Nephrotic syndrome and hepatitis due to acquired syphilis: an uncommon presentation of a re-emerging disease. NDT Plus. 2011;4(1):67–70. ISSN 1753-0784. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25984108
62. Sciaudone M, Rutstein SE, Farel CE. Syphilis-associated acute renal failure and hepatitis in the setting of human immunodeficiency virus coinfection. Sex Transm Dis. 2019;46(12):816–8. ISSN 1537-4521. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31764769
63. Koganemaru H, et al. A case of secondary syphilis demonstrating nephrotic syndrome and a solitary intrahepatic mass in a human immunodeficiency virus-1-infected patient. J Infect Chemother. 2015;21(1):62–4. ISSN 1437-7780. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25127155
64. Jaunin E, et al. Syphilis and parvovirus B19 co-infection imitating a lupus nephropathy: a case report. Medicine (Baltimore). 2019;98(36):e17040. ISSN 1536-5964. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31490394
65. Wanderley DC, et al. The immunohistological profile of membranous nephropathy associated with syphilis infection. Clin Kidney J. 2021;14(7):1857–8. ISSN 2048-8505. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34221395
66. Yang C-C, Chen J-Y, Chang H-Y, Sheu M-J, Feng I-C, Wang S-H, Kuo H-T. Cholestatic Hepatitis with Concomitant Nephrotic Syndrome due to Secondary Syphilis in a Young Man. Case Report Gastroenterol. 2024;18(1):136–43. https://doi.org/10.1159/000537922.
67. Doppalapudi HB, Caraballo LB, Vanguri VK, Basil K. A case of syphilis-induced secondary membranous nephropathy: PUB290. J Am Soc Nephrol. 2023;34(11S):1129. https://doi.org/10.1681/ASN.20233411S11129c.

68. Fan SL, Landgren A, Ruderman I. Syphilis as the great mimicker: a case of full-house pattern membranous nephropathy. Nephrol Primeira publicação. 2023;18 https://doi.org/10.1111/nep.14240.
69. Spaltenstein M, Humbert F, Vu DL, et al. A case report of CT-diagnosed renal infarct secondary to syphilitic aortitis. BMC Infect Dis. 2017;17:520. https://doi.org/10.1186/s12879-017-2624-1.
70. Obimah R, Martinez-Uribe O, Helzberg JH, Gagliardi J, Kappus M. S3847 secondary syphilis can simultaneously mimic primary biliary cholangitis and glomerular nephropathy. Am J Gastroenterol. 2023;118(10S):S2463. https://doi.org/10.14309/01.ajg.0000965028.21324.6e.

Part VII

Chronic Diseases, Transplantation and Interface with Tropical Nephrology

33 Kidney Function Evaluation in Tropical Diseases

Geraldo Bezerra da Silva Junior, Elvino Barros, Gabriela Moreira Ferle, Pedro Guimarães Pascoal, João Filipe Cavalcante Uchoa Furtado, Pedro Vianna Caldas Ribeiro, Elizabeth De Francesco Daher, and Francisco Veríssimo Veronese

33.1 Introduction

The kidneys are responsible for several functions, most of them vital, which aim to maintain the body's balance, including glomerular filtration, urinary concentration, maintenance of body volume, excretion of metabolism products such as creatinine, potassium, urea, acid uric, nonvolatile acids, and others [1–3]. The kidneys are also crucial in excreting exogenous substances that are not part of the body's normal metabolism, such as antibiotics, iodine contrasts and water-soluble drugs, among many other substances. They are considered endocrine organs responsible for the production of erythropoietin, a fundamental hormone in the production of red blood cells by the bone marrow, of renin, 1,25-dihydroxycolecalciferol (vitamin D), prostaglandins, and kinins. They also function as effectors of hormones produced by different body glands: arginine vasopressin (AVP, or antidiuretic hormone) by the pituitary gland, adrenal aldosterone by the adrenal glands, and parathormone (PTH) by the parathyroid glands [1–3].

Kidney function assessment is fundamental in a variety of clinical settings, including tropical diseases, where kidney involvement is often observed, as will be shown in greater detail in this book. Many of the infectious diseases that occur in the tropical regions of the globe are considered as neglected diseases because they are associated with poverty, lack of basic sanitation, access to water, healthy food and even access to health care. Tropical diseases are frequently associated with kidney function loss, and then evaluation of kidney function is essential for the correct management of the patients [4]. This chapter discusses the main methods for assessing renal function, focusing on tropical diseases.

G. Bezerra da Silva Junior (✉) · J. F. C. U. Furtado · P. V. C. Ribeiro
School of Medicine, Universidade de Fortaleza, Fortaleza, Ceara, Brazil
e-mail: geraldobezerrajr@unifor.br

E. Barros · G. M. Ferle · P. G. Pascoal · F. V. Veronese
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil
e-mail: ppascoal@hcpa.edu.br; fveronese@hcpa.edu.br

E. De Francesco Daher
Department of Internal Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_33

33.2 Clinical Assessment of Kidney Function (Glomerular Filtration)

Glomerular filtration is the kidneys' main function, and the glomeruli are responsible for this complex process. The kidneys produce approximately 180 liters of glomerular filtrate per day, the first step for urine formation. Glomerular filtration (GF) is defined as the ultrafiltrate of plasma that crosses the glomerular barrier into the urinary space, expressed in mL/min. The Glomerular Filtration Rate (GFR) is the sum of glomerular filtration of all nephrons and reflects the overall renal function.

The GFR is widely accepted as the best kidney function measure. Under normal conditions, GFR is constant over time, but it decreases with age, as a result of kidney senescence. GFR measurement allows an individual's kidney function to be measured or estimated. It is the most accurate test to establish a normal kidney function, and when chronic function loss occurs, its measurement allows the classification of the chronic kidney disease (CKD) stage, monitors kidney disease progression and the response to the implemented treatment, and allows correct adjustment of drug doses / intervals, reducing the potential risk of nephrotoxicity [2, 3].

33.3 Methods and Equations That Estimate Glomerular Filtration Rate

Serum creatinine, a product of muscle metabolism, is 85–90% filtered in the renal tubules and represents the most frequently used and most practical marker for renal function assessment. It is a low-cost measure available in almost all laboratories. Measurements of creatinine clearance, called endogenous creatinine clearance (ECC) requires 24-h urine collection. Although simple, this process is the main factor of error when assessing renal function, since the collection of urine is usually inadequate [2, 3]. And, most importantly, ECC does not accurately estimate GFR and thus, its use is no longer recommended.

> One way to determine the accuracy of 24-h urine collection is by analyzing the total creatinine excretion in the urine. In men, 20–25 mg of creatinine/kg body weight is expected and in women, 15–20 mg/kg body weight.

Creatinine may overestimate the GFR because its presence in the urine exceeds the amount that has been actually filtered, especially in the presence of CKD, where tubular secretion may be higher than usual. Higher extrarenal excretion, secretion and degradation in the gastrointestinal tract may also occur [2, 3]. It is important to remember that individuals with reduced muscle mass, women, children, and amputated individuals, when there is significant muscle loss, have a lower creatinine production. In these situations, serum creatinine-based GFR measurement may not reflect true GFR. Moreover, serum creatinine is considered a late marker of kidney injury, since its elevation occurs when there is a loss of more than 50% of kidney function. For these reasons, in recent years, much has been invested in the research of new kidney injury biomarkers that can detect injuries earlier, also in the context of tropical diseases [5–9].

33.4 Equations Used to Estimate Renal Function Based on Serum Creatinine Levels

Glomerular filtration rate can be estimated by different mathematical equations developed in different population groups. These are practical equations for daily clinical use and show reasonable correlation with true GFR, as measured by inulin or more accessible radioisotope methods, such as ^{125}I-iothalamate, ^{99m}Tc-DTPA, ^{51}Cr-EDTA, and nonradioactive contrast agent, iohexol. It is recommended that serum creatinine be measured and GFR be estimated for every patient with trop-

ical diseases, considering the frequency of renal involvement. In the near future, it is possible that new, more sensitive and earlier biomarkers than creatinine will be available in medical practice for renal function assessment.

The main formulas used to estimate GFR are as follows:

- *Cockroft and Gault Formula*

Until the late 1990s, it was the most frequently used equation to assess kidney function [10]. It is a simple formula that uses serum creatinine, weight, gender, and age, and it is easily calculated, using a simple calculator. It has some limitations, especially because of the presence of weight in the formula, which may overestimate the creatinine clearance in obese patients or those with edema. Additionally, as it correlates with ECC, it usually overestimates GFR due to the occurrence of tubular creatinine secretion, thus not being the most appropriate for use in clinical practice.

- *Modification of Diet in Renal Disease (MDRD)*

The MDRD equation was published in 1999, developed from a large North-American multicenter study, the "Modification of Diet in Renal Disease" (MDRD) [11]. It allows adjustment according to body surface area and its simplified version only includes age, gender, ethnicity, and serum creatinine data. The main limitation of MDRD is to underestimate GFR in individuals with normal or near-normal renal function, partially because this formula was developed from patients with chronic kidney disease.

- *Chronic Kidney Disease Epidemiology (CKD-EPI)*

It was developed in 2009, and used the same parameters of age, gender, ethnicity, and serum creatinine. It was created based on data from several studies, including individuals with the full spectrum of GFR. Several studies have shown that the CKD-EPI equation shows a better performance, when compared to the MDRD equation, especially in the presence of normal or near-normal glomerular filtration rate (GFR: 60 mL. min^{-1}.1,73 m^{-2}) with lower bias and greater accuracy [12–14]. However, both equations show limitations in estimating GFR in diabetic patients and young individuals. The current recommendation is that all laboratories, when asked to measure serum creatinine levels, should calculate and release the estimated GFR by the MDRD and CKD-EPI equations [12–14]. The CKD-EPI formula was updated in 2021 by eliminating the race coefficient, a change endorsed by The National Kidney Foundation. This decision was made to address the true racial diversity of the population and to avoid limiting access to healthcare for any specific group [15].

These formulas are available for free on electronic calculators on websites such as the Brazilian Society of Nephrology (www.sbn.org.br/utilidades/calculadoras) and the National Kidney Foundation (https://www.kidney.org/professionals/kdoqi/gfr_calculator)

There are also smartphone apps (medical calculators) that contain GFR estimation formulas that can be easily utilized (https://www.mdcalc.com/) and also help patients understand their risk for kidney disease, such as the Renal Health app (https://apps.apple.com/br/app/renal-health/id1485397798)

33.5 Recommendations to Better Estimate Renal Function Through Glomerular Filtration Rate in Clinical Practice

Currently, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend the use of serum creatinine-based CKD-EPI equation to estimate renal function in clinical practice

[16]. Based on this GFR estimate, doses and dose intervals of drugs that have renal excretion should be adjusted and the exposure to contrast media in imaging tests should be more safely planned, aiming at providing nephroprotection [17, 18].

The strategy of preventing acute kidney injury and additional chronic damage in susceptible patients, such as those with chronic kidney disease, is of utmost importance in medical practice. There are websites that guide dose adjustment according to kidney function:

https://www.aafp.org/afp/2007/0515/p1487.html
http://www.globalrph.com/renaldosing2.htm

Another biomarker to be used for GFR estimation is cystatin C, which is freely filtered by the glomeruli and not secreted into the tubules, although it has a small extrarenal clearance. One advantage over creatinine is that cystatin C is less influenced by age and does not depend on the production by muscle mass [19, 20]. The CKD-EPI equation based on cystatin C was developed in 2008, and in 2011, serum cystatin C measurement was standardized, based on calibration that was performed according to international reference standards [19, 20].

The CKD-EPI Cystatin-C equation alone is as precise as the creatinine-based CKD-EPI, with the advantages of not requiring ethnicity specification and being more accurate in individuals with reduced muscle mass [19, 20]. The CKD-EPI equation that combines the two filtration markers, creatinine and cystatin-C, seems to be even more accurate than the other previously described formulas, and can be considered a confirmatory test in individuals with GFR reduction estimated by the other equations.

The main limitation of using cystatin-C is its high cost, which restricts its use as an estimate of renal function in clinical practice. The formulas for estimating GFR are summarized in Table 33.1 [21].

33.6 Tubular Function Assessment

Tubular function comprises the reabsorption and secretion of substances, predominantly water and electrolytes, in addition to regulating the mechanisms of urinary concentration and acidification. Tubular function can be divided according to the segment into:

(a) Proximal tubule: Reabsorbs 100% of filtered glucose and amino acids, 60–70% of water, sodium, phosphate, and bicarbonate, and it is the site where the endocytosis of filtered proteins occurs.
(b) Loop of Henle: Complements the absorption of the proximal segment to adjust the flow of

Table 33.1 Equations that estimate glomerular filtration rate (GFR) based on serum creatinine and cystatin C

MDRD Equation $eGFR = 186.3 \times sCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female gender) $\times$ 1.21 (if Black ethnicity)
CKD-EPI Equation with creatinine $eGFR = 142^{*} \min(sCr/\kappa, 1)^{a*} \max({}_{s}Cr/\kappa, 1)^{-1.2000}\ 0.9938^{age}\ 1.012$ (if female gender) κ, 0.7 if female gender or κ, 0.9 if male gender; α, −0.241 if female gender or α, −0.302 if male gender; min, minimum value of sCr/κ or 1; max, maximum value of sCr/κ or 1
CKD-EPI Equation with cystatin-C $eGFR = 133 \times (sCystC/0.8)^{-0.499} \times 0.996^{age} (\times 0.932 \text{ if female gender}) sCystC \le 0.8$ $eGFR = 133 \times (sCystC/0.8)^{-1.328} \times 0.996^{age} (\times 0.932 \text{ if female gender}) sCystC > 0.8$
CKD-EPI Equation with creatinine + cystatin-C $eGFR = 135 \times \min(sCr/\kappa,1)^{\alpha} \times \max(sCr/\kappa,1)^{-0.544} \times \min(sCystC/0.8,1)^{-0.323} \times \max(sCystC/0.8,1)^{-0.778} \times 0.9961^{age} \times 0.963$ (if female gender) $\kappa = 07$, (women) or 0.9 (men); $\alpha = -0.219$ (women) or −0.144 (men)

eGFR estimated glomerular filtration rate (mL/min/1.73 m^2), *sCr* serum creatinine (mg/dL), *sCystC* serum cystatin-C

water, sodium, magnesium, and calcium in the distal tubule, and initiates the potassium and $NH4^+$ osmotic gradient mechanism.

(c) Distal twisted tubule: where a quantitatively small resorption occurs, less than 10% of the load filtered by the glomerulus, but qualitatively important.

(d) Collecting duct: The main site of water and potassium excretion and distal acid secretion, depending on the osmotic, potassium and $NH4^+$ gradient [22].

It is important to review tubular physiology to understand some changes observed under certain pathological conditions. Many tropical diseases occur simultaneously with tubular dysfunction, such as leptospirosis [23], visceral leishmaniasis [24], American cutaneous leishmaniasis [25], schistosomiasis [26], which are often asymptomatic and may persist even after specific infection treatment [23, 27]. Kidney tubular defects are described in patients with visceral leishmaniasis, including tubular acidosis [28]. GFR reduction usually occurs late during the course of kidney disease, whereas tubular alterations occur earlier. Moreover, tubulointerstitial alterations, such as tubular fibrosis and atrophy, have a strong correlation with poor prognosis, even more than glomerular lesions [22].

The assessment of kidney tubular function has two main indications:

- Investigation of primary tubular diseases.
- Detection of early tubular alterations during the course of glomerular diseases (in this case, in the context of tropical diseases, which can often cause tubulointerstitial lesions and asymptomatic tubular disorders).

The following are some formulas and guidelines for tubular function assessment, which should be investigated whenever the objective is to fully characterize renal function and when tubular lesion is suspected.

Fractional excretion of sodium ($FENa^+$)

$$FENa^+ = \left(UNa^+ / PNa^+\right) / \left(Ucr / Pcr\right) \times 100$$

Transtubular potassium gradient (TTKG)

$$TTKG = \left(Posm \times UK\right) / \left(PK \times Uosm\right), \text{where}$$

where,

UNa^+ and UK^+: Urinary concentration of sodium and potassium

PNa^+ and PK^+: Plasma concentration of sodium and potassium

Ucr and Pcr: Urinary and plasma creatinine concentration

Uosm and Posm: Urinary and plasma osmolarity expressed in mOsmol / kg. H_2O

Urine/plasma osmolarity ratio:

Uosm/Posm

Solute-free water transport:

$$TcH_2O = Cosm - V$$

Cosm → Uosm.V/Posm

V → Urinary volume in L/day

Uosm and Posm: Urinary and plasma osmolarity expressed in mOsmol / kg. H_2O.

Plasma Osmolarity:

$$Posm = 2 \times Na + +Glyc / 18 + BUN / 2.8$$

Posm: plasma osmolarity

Na^+: plasma Sodium

Glyc: Fasting Glycemia

BUN: Blood urea nitrogen (BUN), obtained by dividing plasma urea by 2.14.

Plasma osmolarity is expressed in mOsmol/kg. H_2O.

Urinary acidification test:

The urinary acidification test has been used for decades to evaluate one of the kidney tubular functions. It was classically designed with the use of ammonium chloride (NH_4Cl) for 3–5 days [29]. Some patients do not tolerate the use of this salt, so an alternative agent, calcium chloride ($CaCl_2$) may be used. Studies comparing the efficacy of both agents in hospitalized individuals to assess urinary acidification capacity have found a similar response with NH_4Cl, which may be recommended for clinical investigation [30, 31]. Patients go on an absolute fast after 7 p.m. on the night before the test. On the day of the test, patients should collect the first urine sample (T0) and a venous blood sample to measure pH and bicarbonate levels. Then, the acid agent (NH_4Cl

or $CaCl_2$) is ingested. After the salt intake, the patients remain under observation and fasting for 4 h. At the fourth hour (T4) after the salt intake, a new urine sample is obtained to measure urinary pH (UpH). Urinary acidification deficit is considered as the incapacity to reduce urinary pH to less than 5.5, after an acid overload.

Urinary Concentration Test:

The urinary concentration test is another method for kidney tubular function assessment that evaluates distal nephron function. Uosm (T4) >700 mmOsm/kg/H_2O are used as reference values for the maximum urinary concentration [32–34]. On the day of the test, patients should collect the first morning urine sample, after a 12-h period of water deprivation, and this urine sample is used to measure the urinary osmolarity (Uosm).

In short, kidney function assessment is of utmost importance in tropical diseases, since kidney involvement is a frequent occurrence, both glomerular and tubulointerstitial involvement. There are several methods for renal function assessment, with the most widely used in current practice being serum creatinine measurement and glomerular filtration estimation. New biomarkers of kidney injury are being investigated and may be used in the future as earlier markers of renal impairment in tropical diseases.

References

1. Barros E, Thomé FS, Karohl C. Fisiologia renal aplicada. In: Nefrologia. Rotinas, diagnóstico e tratamento. 2ª ed. Porto Alegre: ArtMed; 1999. p. 25–46.
2. Eaton DC, Pooler JP. Fisiologia Renal de Vander. 8ª ed. Porto Alegre: AMGH; 2016.
3. Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL, editors. Brenner and Rector's the kidney. 10th ed. Philadelphia: Elsevier Saunders; 2016.
4. Silva Junior GB, Jereissati AAR, Neri AKM, Lino DOC, Oliveira JGR, Daher EF. Neglected tropical diseases with an impact on kidney function. In: Rodríguez-Morales AJ, editor. Current topics in tropical emerging diseases and travel medicine. London: IntechOpen; 2018. p. 31–47.
5. Meneses GC, Cavalcante MG, Silva Junior GB, Martins AMC, Neto RDJP, Libório AB, Daher EF. Endothelial glycocalyx damage and renal dysfunction in HIV patients receiving combined antiretroviral therapy. AIDS Res Hum Retroviruses. 2017;33(7):703–10.
6. Meneses GC, Daher EF, Silva Junior GB, Libório AB, Martins AC. Serum neutrophil gelatinase-associated lipocalin levels predict acute kidney injury in visceral leishmaniasis [abstract]. J Am Soc Nephrol. 2016;27(Suppl):242.
7. Santos TE, Gonçalves RP, Barbosa MC, Silva Junior GB, Daher EF. Monocyte chemoatractant protein-1: a potential biomarker of renal lesion and its relation with oxidative status in sickle cell disease. Blood Cells Mol Dis. 2015;54(3):297–301.
8. Libório AB, Braz MB, Seguro AC, Meneses GC, Neves FM, Pedrosa DC, Cavalcanti LP, Martins AM, Daher EF. Endothelial glycocalyx damage is associated with leptospirosis acute kidney injury. Am J Trop Med Hyg. 2015;92(3):611–6.
9. Meneses GC, Libório AB, Daher EF, Silva Junior GB, Costa MF, Pontes MA, Martins AM. Urinary monocyte chemotactic protein-1 (MCP-1) in leprosy patients: increased risk for kidney damage. BMC Infect Dis. 2014;14:451.
10. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–4.
11. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247–54.
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
13. Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis. 2010;55:648–59.
14. Veronese FV, Gomes EC, Chanan J, Carraro MA, Camargo EG, Soares AA, Thomé FS, Silveiro SP. Performance of CKD-EPI equation to estimate glomerular filtration rate as compared to MDRD equation in South Brazilian individuals in each stage of renal function. Clin Chem Lab Med. 2014;52:1747–54.
15. Meeusen JW, Kasozi RN, Larson TS, Lieske JC. Clinical impact of the Refit CKD-EPI 2021 creatinine-based eGFR equation. Clin Chem. 2022;68(4):534–9. https://doi.org/10.1093/clinchem/hvab282. PMID: 35038721.
16. National Kidney Foundation (NKF). Kidney disease outcome quality initiative (K/DOQI) advisory board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Part 4. Definition and classification of stages of chronic kidney disease. Am J Kidney Dis. 2002;39(Suppl 2):S46–75.

17. Czock D, Bertsche T, Haefeli WE. Drug adjustments in patients with renal impairment. Am J Kidney Dis. 2009;54(5):983–4.
18. Doogue MP, Polasek TM. Drug dosing in renal disease. Clin Biochem Rev. 2011;32(2):69–73.
19. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis. 2008;51:395–406.
20. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367:20–9.
21. National Kidney Foundation. CKD-EPI Creatinine Equation (2021) and CKD-EPI Creatinine Equation (2021). 2024. Retrieved from https://www.kidney.org/content/ckd-epi-creatinine-equation-2021.
22. Blanchard A, Poussou R, Houillier P. Exploration des fonctions tubulaires rénales. Nephrol Ther. 2009;5(1):68–83.
23. Daher EF, Zanetta DM, Abdulkader RC. Pattern of renal function recovery after leptospirosis acute renal failure. Nephron Clin Pract. 2004;98(1):c8–14.
24. Oliveira MJ, Silva Junior GB, Sampaio AM, Montenegro BL, Alves MP, Henn GA, et al. Preliminary study on tubuloglomerular dysfunction and evidence of renal inflammation in patients with visceral leishmaniasis. Am J Trop Med Hyg. 2014;91(5):908–11.
25. Oliveira RA, Diniz LF, Teotônio LO, Lima CG, Mota RM, Martins A, et al. Renal tubular dysfunction in patients with American cutaneous leishmaniasis. Kidney Int. 2011;80(10):1099–106.
26. Duarte DB, Vanderlei LA, Bispo RK, Pinheiro ME, Silva Junior GB, Martins AM, et al. Renal function in hepatosplenic schistosomiasis – an assessment of renal tubular disorders. PLoS One. 2014;9(12):e115917.
27. Daher EF, Rocha NA, Oliveira MJ, Franco LF, Oliveira JL, Silva Junior GB, et al. Renal function improvement with pentavalent antimonial agents in patients with visceral leishmaniasis. Am J Nephrol. 2011;33(4):332–6.
28. Lima Verde FA, Lima Verde FA, Lima Verde IA, Silva Junior GB, Daher EF, Lima Verde EM. Evaluation of renal function in human visceral leishmaniasis (kala-azar): a prospective study on 50 patients from Brazil. J Nephrol. 2007;20(4):430–6.
29. Wrong O, Davies HE. The excretion of acid in renal disease. Q J Med. 1959;28:259–313.
30. Oster JR. A short duration renal acidification test using calcium chloride. Nephron. 1975;14:281–92.
31. Kurtzman N. Acquired distal renal tubular acidosis. Kidney Int. 1983;24:807–19.
32. Rado JP. 1-desamino-8-D-arginine vasopressin (DDAVP) concentration test. Am J Med Sci. 1978;275:43–52.
33. Abyholm G, Monn E. Intranasal DDAVP-test in the study of renal concentrating capacity in children with recurrent urinary tract infections. Eur J Pediatr. 1979;130:149–54.
34. Tryding N, Sterner G, Berg B, Harris A. Subcutaneous and intranasal administration of 1-deamino-8-d-arginine vasopressin in the assessment of renal concentration capacity. Nephron. 1987;45:27–30.

34 Kidney Disease of Unknown Origin and Tropical Diseases

Maristela Böhlke, Viviane Calice-Silva, Eduardo Ribes Kohn, Pedro Böhlke Barcellos, Carmen Lorena Cajina Aguirre, and Roberto Pecoits-Filho

34.1 Introduction

Kidney disease is a growing concern for global public health. It is estimated that more than 850.000.000 persons worldwide have some form of kidney impairment, encompassing both chronic and acute diseases [1]. Two-thirds of these patients suffer from chronic kidney disease (CKD), being estimated that 80% of them live in low-income (LIC) and lower-middle-income countries (LMIC), within tropical regions [1, 2]. The incidence rate of CKD in these countries is estimated to be four to five times higher than in high-income countries (HIC), and the affected individuals are typically younger [3, 4]. The adoption of Western diets, the increasing use of toxic agrochemicals, changing demography, and genetic inheritance have all contributed to this surge in CKD among economically vulnerable countries. Despite the higher prevalence of CKD in LIC and LMIC, 90% of those receiving kidney replacement therapy (KRT) live in HIC and upper-middle-income countries (UMIC). Awareness of the disease is limited, and KRT is not widely available in most tropical countries. As a result, this health inequity involves poor economic conditions and kidney disease intertwined in a vicious cycle of impoverishment and illness.

While most cases of CKD are caused by diabetes, glomerulonephritis, HIV, and obstructive uropathy, approximately 20% of the cases have no identified source, even in HIC [5]. The nomenclature CKD of unknown origin (CKDu) or CKD of nontraditional causes (CKDnt) have been recently introduced to describe these cases of CKD where the cause was not identified after a complete diagnostic workup [6].

34.2 Epidemiology of CKDu in Tropical Countries

There are scant epidemiological data on CKD in most LIC and LMIC due to few community-based studies, inconsistent assessments of kidney

M. Böhlke (✉) · P. B. Barcellos
Catholic University of Pelotas,
Pelotas, Rio Grande do Sul, Brazil
e-mail: maristela.bohlke@ucpel.edu.br

V. Calice-Silva
Univille School of Medicine, Pro-Rim Foundation and Hospital Hans Dieter Schimidt,
Joinville, Santa Catarina, Brazil

E. R. Kohn
Palacky University Olomouc, Olomouc, Czechia

C. L. C. Aguirre
The University of Kansas Medical Center,
Kansas City, KS, USA

R. Pecoits-Filho
Arbor Research Collaborative for Health,
Ann Arbor, MI, USA

School of Medicine, Pontifical Catholic University of Paraná, Curitiba, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_34

function, and a lack of mandatory registries. Awareness about the disease is also very low in most of this region. Most statistics are derived from estimates, not true measures. In this landscape, where the disease per se is poorly diagnosed and registered, the proper etiologic investigation is even rarer, and ascertaining the epidemiology of CKDu is a tough task [4].

There is an underreporting of CKDu even in UMIC and HIC, which may be due to mistakenly attributing diabetes or hypertension [7] as the source of CKD in patients who suffer from these conditions. These assumptions have led the KDIGO 2020 guideline to emphasize that the cause of CKD should not be assumed solely based on the presence of comorbidities [6]. The 2014 ERA-EDTA Registry [8] labeled 19% of the patients starting maintenance KRT as cases of CKDu. This percentage increased to 26% in the 2019 Registry [9], with a proportional decrease in cases attributed to high blood pressure. In registries from Brazil and other tropical LIC and LMIC, the percentage of CDKu remains steady at around 10% [10]. This is likely due to the lack of mandatory registries (or the lack of registries altogether) and the persistent practice of attributing the cause of CKD to existing comorbidities, particularly hypertension (which is often a consequence rather than the cause of kidney disease). In Brazil, the registry is optional and collects data from the dialysis unit rather than from individual patients. Moreover, it typically manages to gather data from fewer than half of the Brazilian dialysis units [10].

34.2.1 Tropical Hotspots for CKDu

The prevalence of CKDu is exceptionally high in certain regions, mainly located in tropical LIC and LMIC. These CKDu hotspots create significant public health challenges and lead to the loss of a productive workforce, reduced life expectancy, and considerable personal suffering, further exacerbating economic hardship in these communities. Despite the unknown source, the similarities in epidemiology, risk factors, and clinical, laboratory and histological presentation raise a strong suspicion of a unifying cause or group of causes [11, 12]. Corroborating this hypothesis, some previous CKDu hotspots have already identified the source of the disease, such as the case of Balkans nephropathy, which was found to be caused by Aristolochic acid contaminated crops [13], and Itai-Itai Disease from Japan, caused by chronic cadmium exposure [14]. In some other areas heavily affected by CKDu, the causes remain unidentified. Regions in Central America (such as El Salvador, Nicaragua, and Guatemala) and South Asia (including Sri Lanka and India) have been dealing with this widespread endemic CKDu since the 1990s, posing one of the most significant public health crises in recent years [15].

34.2.1.1 Central America

Central America is located entirely within the Earth's tropical region, between the Cancer and Capricorn tropics. The region presents high humidity and tropical climates, mainly comprising LIC and LMIC. Since the 1990s, an increasing incidence of CKDu in the region has been described, affecting predominantly younger rural workers on the Pacific coast of El Salvador [16], Guatemala and Nicaragua [17]. The kidney disease in this hotspot was called Mesoamerica endemic Nephropathy (MeN) [18].

El Salvador

El Salvador presents the second highest CKD-related mortality rate in the Americas, estimated at 72.9 deaths/100,000 inhabitants, being the second major cause of death among men of 18 years or older [15]. The prevalence of KRT is described as 882 ppm. Moreover, this region has experienced a >50% increase in the age-standardized disability-adjusted life-years (DALY) attributable to CKD from 1990 to 2017, diverging from the global trend. In the country, the rate of patients on KRT in 2018 was 677 per million inhabitants, exceeding the regional rate for Central America and the Caribbean (392 per million inhabitants). In 2023, 62% of the kidney failure patients were treated by peritoneal dialysis and 37% by hemodialysis.

Guatemala

The neighboring Guatemala, an UMIC, faces similar challenges. Although public funding for KRT is available in Guatemala, there are fewer than five nephrologists per million of the population in the country, most of them clustered in a handful of urban centers. Almost half of the Guatemaltecos are of Mayan ancestry, speaking only the Mayan dialect and living in poor rural areas far from urban centers. To compensate for these geographical barriers, almost 50% of kidney failure patients are treated by peritoneal dialysis. However, concerns regarding KRT access in Guatemala remain. The overall prevalence of KRT in the country is 536 pmp. However, the huge disparity between employer-funded health insurance (1265 pmp), and that provided to patients who lack health insurance (388 pmp), who respond for around 60% of the adult Guatemalan population, give way to concerns about under-detection and insufficient treatment of kidney failure, as well as underestimation of CKD-related mortality.

Nicaragua

In Nicaragua, kidney disease is the second leading cause of death nationwide, estimated in 2019 at 73.9 deaths/100,000 population. Nicaragua has been affected by a concerning rising mortality rate secondary to CKD. Between 1990 and 2009, CKD mortality increased approximately threefold [1]. Besides significant causes such as hypertension and diabetes, CKDu has previously been recognized as a significant contributor [2].

Within the country, CKDu is characterized by its geographic distribution, which has hotspots in the Pacific region [3]. Despite the lack of official national data, different community-based studies have reported 14–18% prevalences in young males in the Northwest area. However, some authors have observed higher prevalences of up to 40% in communities historically affected by CKDu [4]. These differences depend on different factors such as location, occupation, and age. Researchers have identified risk factors such as agrochemical exposure, heat stress, dehydration, heavy metals, nonsteroidal anti-inflammatory drugs, nephrotoxic antibiotics, lower socioeconomic status, drinking well water, low body mass index, and infections like Leptospira [5].

Treatment of CKDu usually starts in the later stages of CKD, once complications have been established. Currently, kidney failure treatment in Nicaragua is based on the modality of HD, which has significantly increased in recent years. This increment paralleled a decrease in patients receiving peritoneal dialysis, which was reported as 2.1% in 2023 [8, 9]. Kidney transplants remain uncommon with less than 2 pmp [8]. Also, rural areas most affected by CKDu lack resources, with most dialysis centers located in urban areas, making access challenging for these populations [8]. Additionally, Nicaragua has the lowest nephrologist density in Latin America. This disparity in healthcare access highlights the urgent need to address the growing burden of CKDu in Nicaragua [10].

34.2.2 South Asia

Another CKDu hotspot was described in South Asia, affecting regions with characteristics similar to Central American hotspots, including low altitudes, low humidity, and tropical climates [19]. The disease in both regions was unified by the Chronic Interstitial Nephritis in Agricultural Communities (CINAC) designation. The most severely impacted areas include the Central North Province of Sri Lanka and certain regions in India, such as Andhra Pradesh.

34.2.2.1 Sri Lanka

The prevalence rate of CKDu in Sri Lanka has been estimated by some community-based studies in the endemic areas and, according to the region and the definition of CKDu has varied between 11% of men and 4% of women in the North Central Province [19] to 15% in the districts of Anuradhapura, 20% in Polonnaruwa, and 23% in Badulla [20].

Both affected and nonaffected villages share similar lifestyles, cultural habits, and socioeconomic conditions. The key differences lie in significantly higher rates of malnutrition and lower quality of drinking water in the affected regions [21]. It is alarming that as many as nine out of ten

individuals with CKD in resource-poor settings with weak primary care infrastructure are unaware of their condition and, as a result, do not seek treatment [22]. Additionally, over a third of those affected do not receive Western medical treatment because they refuse to attend government clinics and hospitals, and approximately half die at home. This denial is partly caused by economic costs, travel difficulties, and inconvenience, or attempts to minimize the societal stigma associated with the disease [23]. Thus, the Department of Health's annual morbidity and mortality statistics (exclusively derived from hospital data) capture fewer than half and are significantly inaccurate. Data on the prevalence of treated KF were not available. The prevalence of HD, PD, and kidney transplantation centers is 2.76, 0.22, and 0.60 pmp, respectively. These procedures are funded by a mix of public and private sectors and out-of-pocket expenditures for KRT, except for PD, which was covered entirely by public funds [24].

34.2.2.2 India

In India, there is a paucity of data on the incidence and prevalence of CKD in the national registry. Although the accurate burden of CKD in India is lacking, some regions seem to present a higher-than-expected prevalence of the disease. Uddanam is a primarily agricultural region in coastal Andhra Pradesh known for its coconut and cashew plantations. A population-based report from India shows an 18% CKD prevalence in this region, with 70% of cases meeting CKDu criteria [25]. A high prevalence of CKDu has also been reported in the Canacona taluk of Goa in South India, with one study reporting that 12.1% of participants in a medical screening camp had CKD, with urolithiasis in 40.9% and urinary abnormalities in 24.2% [26]. Another potential hotspot is the Cuttack district in Odisha, Eastern India, with a reported prevalence of chronic kidney disease (CKD) at 14%, of which 70% are cases of CKDu [27].

34.2.3 Egypt

Egypt lacks a national CKD registry. However, local inquiries reveal that the prevalence of CKD in the El-Minia Governorate increased from 250 patients per million in 2002 to 308 per million in 2006. Approximately 27% of the patients on dialysis had no identifiable cause for CKD [28].

34.2.4 Mexico

In Tierra Blanca, Veracruz, Mexico, a 25% prevalence of CKD has been reported among individuals aged 20–60 years, with 44% classified as having CKDu [29]. Another CKDu hotspot in Mexico is Poncitlan in Jalisco. The reported prevalence of CKD in Poncitlan is 20%, which is higher than the 10.4% reported in other municipalities in the same state [30]. In the state of Aguascalientes, 73% of patients included in a kidney failure registry had CKD with no identifiable etiology. These patients are aged between 20 and 30 years old, and focal and segmental glomerulosclerosis was the most common pathology among those who underwent kidney biopsy (in contrast to the predominant tubulointerstitial involvement in other forms of CKDu) [31].

34.2.5 CKDu in Sub-Saharan Africa

There are limited data on the prevalence, incidence, and cause of CKD in sub-Saharan Africa due to poor sampling methods in observational studies, unreliable kidney function measurements, and lack of registries [32]. Although diabetes, HIV, and other infections are the main contributing factors to CKD in Africa, there are reports of excess risk of CKD not explained by traditional risk factors [33]. In Nigeria, up to 50% of the cases of CKD had no cause determined [34]. In Senegal, CKD etiology is also dominated by unknown causes (34%), which can be even higher due to 25% of the cases being attributed to high blood pressure [35]. Among the few people that had access to HD in Ethiopia (RRT prevalence 10 ppm in 2021, compared to 2219 pmp in the USA in the same year), 37% was declared as unknown primary cause of CKD, and another 48% was attributed to high blood pressure [36]. In Sudan, 53% of the patients on maintenance HD had DRCu [37]. High blood pressure has been documented as the main cause of KRT

(33.1%) in Somalia, and 24.4% of the cases are attributed to CKDu [38]. In one of the larger population surveys on the prevalence of markers for kidney damage in sub-Saharan African countries, including around 8000 individuals, CKDu accounted for 36.5% of the CKD burden [39].

The higher occurrence of chronic kidney disease, including CKDu, remains in descendants of emigrated African Blacks. According to the United States Renal Data System 2022 Annual Data Report, 30% of patients on KRT in the USA are Black individuals [40], although they comprise only 13–14% of the population.

34.3 Potential Etiology of CKDu in Tropical Countries

Genetic, environmental, toxic, and infectious causes seem to respond to most CKDu cases in tropical and nontropical countries.

34.3.1 Genetic Disease

The understanding of the genetic basis of several kidney diseases has evolved significantly since 1985, when the locus of the PKD1 and PKD2 genes were identified on the short arm of chromosome 16 [41]. Exome sequence reports suggest that genetic conditions account for up to 25% of the cases of CKDu, with variants in genes causing autosomal dominant tubulointerstitial kidney disease (ADTKD) and encoding type IV collagen responding to almost half of these cases [5, 42, 43].

APOL1-Related CKD The recognition of the relationship between APOL1 gene variants and glomerular disease was particularly important for tropical countries [44]. APOL-1 belongs to a family of proteins that protects against African sleeping sickness caused by a trypanosome. The identified variants, G1 and G2, provide additional protection against the disease compared to the ancestral G0 allele. The survival advantage of the mutation has led to a high prevalence of the G1 and G2 variants in sub-Saharan Africa, but at a high cost: the long-noted increased frequency of CKD among persons with recent sub-Saharan African ancestry. The APOL-1 variants are associated with a broad spectrum of nephropathies, such as FSGS, HIV-associated nephropathy, and lupus nephritis. However, the presence of the allele variants results in CKD only in a subset of individuals (incomplete penetrance), depending on some contributing factors, such as HIV infection or high interferon states, as well as other unknown factors [45].

34.3.1.1 Sodium-Dependent Dicarboxylate Transporter Member 3 (SLC13A3) and Voltage-Gated Potassium Channel (KCNA10) Polymorphisms

Some genetic factors have been investigated in the tropical hotspots of CKDu to explain the familial clustering of the condition [46] and why kidney disease develops in some but not all workers at risk. The polymorphisms in SLC13A3 [47] and KCNA10 [48] were identified as risk factors in Sri Lankan nephropathy, but the findings require additional investigation.

34.3.2 Environmental and Toxic Causes

The cause of the CINAC is not fully elucidated but probably involves occupational exposure to toxins, heat stress, and dehydration with repeated episodes of acute kidney injury.

Heat Stress The hottest regions of the tropical countries are the most affected by CINAC [49]. Excessive ambient and metabolic heat during exertion increases the body's temperature, leading to sweating and substantial loss of volume, sodium, and potassium. The decrease in plasma volume stimulates vasopressin, catecholamines, cortisol, and the renin-angiotensin-aldosterone system, and the urine will show a prerenal pattern with low urine sodium and potassium loss. The decreased intracellular potassium in the muscles prevents glycogen deposition and may be responsible for rhabdomyolysis [50]. When compensa-

tion fails, and the body's temperatures rise, inflammatory pathways are stimulated, inducing the expression of heat shock proteins and cytokines.

However, it is generally accepted that other risk factors might also be involved because MeN appears relatively recent and geographically restricted. In contrast, exposure to occupational heat stress is not new and is widely distributed around the globe.

Subclinical Rhabdomyolysis Some authors have identified a direct linear correlation between increased serum creatinine, creatine phosphokinase, and myoglobin levels. They have proposed the hypothesis that repeated subclinical episodes of rhabdomyolysis occur daily during the harvest season in sugar cane workers related to CKDu.

Environmental Toxins Other causal hypotheses for CINAC involve environmental toxins associated with genetic predisposition and exposure to dietetic and pharmaceutical agents.

Agrochemicals Nowadays, there is a strong suggestion that the CINAC is associated with the use of pesticides. The increase in cases of CKDu coincides temporally with the industrial escalation of agriculture and widespread importation of pesticides in endemic regions. Women and children who did not directly work on plantations were also affected by the disease, although less frequently than active plantation men workers, which played against the disease being caused only by heat stress and dehydration. In addition, provinces next to the affected ones with more rigid restrictions on pesticide use are scarcely affected or even free from the disease, as occurs with the North Province in Sri Lanka. Recent investigation on tissue analysis of kidney biopsies of CINAC patients has found a proximal tubulopathy with cell cytoplasm showing an accumulation of ingurgitated lysosomes, findings like that found in calcineurin inhibitors tubulopathy [51]. Most nongenetic renal tubulointerstitial diseases are attributed to exposure to chemical nephrotoxins. Some pesticides that knowingly inhibit the calcineurin pathway (paraquat, glyphosate, and pyrethroids) are under investigation.

Heavy Metals in Drinking Water All affected regions have experienced increased daytime average temperatures and prolonged droughts that markedly affect water quality and vegetation, presumably due to climate change. Data suggest that the disease predominantly affects those who consume surface water from shallow wells (and tube wells) located on flat land with higher water-rock interaction [52]. By contrast, drinking water from reservoirs, streams, springs, and canals seems to protect against the disease, which supports a geogenic etiology of the disease. The geographic distribution of the illness is not uniform (nor is the distribution of water content of fluoride or other postulated elements across the region). Frequently, there are clusters of disease-affected households in non-contiguous areas separated by villages with a low CKDu prevalence. Within the North Central Province of Sri Lanka, villagers who consume water from natural springs have the lowest prevalence (less than 2% among adults) of the disease compared with more than 20% in neighboring villages. This further strengthens the hypothesis that, in contrast to food, water is the source of the disease, with a strong emphasis on water chemistry. The mineral characteristic of the water seems also to change the half-life of agrochemicals such as glyphosate [53].

34.3.3 Infectious Diseases

It has been hypothesized that an infectious disease may contribute to the development of MeN and other endemic CKDu.

Leptospirosis Leptospirosis has been a prime suspect, owing to the frequent involvement of the kidney and the prevalence of leptospirosis in the kinds of occupations associated with MeN. Occupational risk groups include agricultural workers, animal husbandry workers, fish workers, miners, and sewer workers, and the bulk of the global disease burden is borne by males aged 20–49 years. Over the past 20 years, multi-

ple outbreaks of leptospirosis have occurred in areas where MeN is frequent, and leptospirosis is now endemic in at least one such area, the Department of Leon in Nicaragua. Presentations of leptospirosis in humans range from asymptomatic to fulminant fatal disease. Cases are often misdiagnosed because of the nonspecific nature of the symptoms. The bacteria penetrate the renal tubules to adhere to their inner surface, causing tubulointerstitial nephritis and tubular dysfunction. Serum creatinine usually returns to normal levels during the second week of illness as the infection is cleared. However, kidney function may continue to deteriorate after AKI, at least in the presence of other contributing factors, increasing the risk of CKD. There is some evidence that chronic or repeated leptospirosis infection is associated with both the prevalence and severity of CKD. However, Yih et al. evaluated 320 adult residents of a gold-mining area in Nicaragua and despite a high rate of Leptospira seropositivity, no association between Leptospira or Hantavirus seropositivity and MeN was found [54].

Hantavirus Hantavirus is another rodent-borne pathogen proposed as a possible causal agent in CKDu. Old World varieties of hantavirus have tended to be associated with hemorrhagic fever with renal syndrome; the Old World Puumala hantavirus is well-known to induce acute tubulointerstitial nephritis and AKI. In Sri Lanka, Gamage et al. found that serology of past exposure to hantavirus was significantly higher among patients with CKDu. Despite New World varieties of hantavirus usually causing cardiopulmonary syndrome, Old World hantaviruses have been reported in the Americas, and novel strains of the virus continue to be identified.

34.4 Clinical Manifestations and Diagnosis

CKDu usually presents in 20–40-year-old males with unexplained decreased kidney function with no history of hypertension or diabetes. It is more prevalent among sugarcane cutters compared to farmers and construction workers. The disease is usually asymptomatic until patients develop ESKD or are first detected due to increased serum creatinine in a health screening. Frequently reported symptoms include muscle cramps, dysuria, urinary frequency, and urgency. On clinical presentation, patients are commonly normotensive, with different laboratory imbalances such as hypokalemia, hypomagnesemia, hyponatremia, and hyperuricemia. Patients also commonly report "chistata," which is a group of symptoms characterized by urgency, burning pain that is exacerbated by urination, and back pain reported as "kidney pain." This is often secondary to extended exposure to high temperatures accompanied by dehydration. Typically, CKDu is characterized by mild proteinuria. The urinary sediment usually reveals white and red cells and sometimes urate crystals [55]. Recent investigation on tissue analysis of kidney biopsies of patients diagnosed with MeN/CINAC has found proximal tubulopathy, with cells' cytoplasm showing an accumulation of ingurgitated lysosomes, like that found in calcineurin inhibitor tubulopathy [51]. The glomeruli may show wrinkling and mesangial expansion with or without global glomerulosclerosis.

There is evidence to suggest that the repeated episodes of AKI that frequently occur in these workers may contribute to causing CKD. An acute form of MeN has been described by Fischer et al. with low-grade fever, nausea, vomiting, headache, and myalgia. The mean rise in serum creatinine (from baseline values) was 2.0 ± 0.6 mg/dL, with leukocyturia, leukocytosis, and neutrophilia in most of these patients. Biopsies show acute interstitial nephritis with tubular injury. At a follow-up of 3 months, 8.5% had progressed to CKD [56].

Most regions affected by CKDu are in LIC and LMIC, so timely diagnosis is crucial to avoid the need for KRT, which is frequently unavailable. However, laboratory resources and access to reliable electricity for establishing a laboratory infrastructure are also limited. Diagnostic tools that facilitate bedside screening may enhance detection, guide treatment, and improve follow-up capabilities. Point-of-care testing (POCT) devices have been evaluated and implemented in

various low-resource areas, demonstrating effective diagnostic performance for kidney disease detection. Some POCT devices can be used alongside smartphones, enabling automatic digitization of results and communication via text message or the internet. These devices can measure biomarkers using blood, plasma, sweat, urine, and saliva samples. The most used laboratory method for assessing kidney function is serum creatinine measurement, which is based on color change resulting from the reaction of creatinine with picric acid in the Jaffe reaction. More recent enzymatic methods have led to the development of small bedside POCT devices, which maintain accuracy while being more accessible. However, these newer methods are more expensive, which may hinder their use in some regions worldwide [57]. POCT devices allow for serum creatinine assessment for AKI and CKD diagnosis and facilitate serial measurements to monitor renal function in low- and middle-income countries or remote areas.

Another significant POCT tested in various populations is the salivary urea nitrogen dipstick (SUN), which has shown good diagnostic performance, particularly at elevated blood urea nitrogen (BUN) levels. The concept of salivary urea nitrogen was first introduced by Wright in 1841, who noted that a patient with a uterine tumor developed ascites and reduced urine output, leading to compensatory urea elimination through saliva. Urea reaches saliva through diffusion, and when combined with bicarbonate, it contributes to the buffering capacity of saliva. In 1922, Hench and colleagues reported a positive correlation between salivary and BUN levels [58]. Their findings indicated that the combination of urea and ammonia nitrogen in saliva averaged 80% of BUN. Subsequently, various researchers measured SUN using different methods, but it wasn't until 1983 that the first study using a test-strip method was conducted by Akai et al. They studied 44 CKD patients and 12 healthy controls with a urease-containing test strip and an automatic reflectance spectrometer. Results indicated a temperature-dependent change in SUN and BUN values, with a saliva/serum ratio of approximately 1.03 [59].

Integrated Biomedical Technology developed a newer dipstick method that allows SUN assessment without additional devices at a low cost (approximately US$1 per test). This method requires transferring 50 μL of saliva to the test pad, where urease cleaves the SUN into ammonia and hydroxyl ions, altering the pH and color of the test pad.

Raimann et al. studied 68 CKD patients, finding a significant correlation between SUN and BUN (RS = 0.63; $p < 0.01$) [60]. The SUN dipstick demonstrated high sensitivity (0.91) and specificity (0.79) for diagnosing AKI [61]. Subsequent studies replicated these findings in various settings, including cases of AKI due to malaria in Angola [62], adult and obstetric patients in Malawi [63], and pediatric patients in Sudan [64].

However, while promising, SUN and BUN do not correlate well at lower BUN levels. Factors such as the composition of the strip buffer relative to saliva pH may contribute to inaccuracies at low levels. Ongoing research is focused on improving the accuracy of measurements at these lower concentrations, and further studies are essential to evaluate the tool's applicability across diverse populations, including healthy individuals and those on multiple medications.

34.5 Prognosis and Treatment

MeN/CINAC The progression of the disease is variable. Some cases diagnosed initially as MeN have shown kidney function recovery, likely representing slowly resolving AKI. In some cases, kidney function remains impaired but stable for years, whereas in others, it progresses to kidney failure or death 3–5 years after diagnosis. Unfortunately, most of the individuals who develop these conditions live in disadvantaged communities and lack adequate medical care, carry no insurance, have no access to proper KRT, and end up dying of kidney failure. DRCu leads to around 30,000 deaths per year in Central America and Sri Lanka, most of them males of productive age.

Increasing evidence suggests that measures to reduce heat stress, such as better hydration,

shade, and rest, can protect individuals from developing cross-shift AKI. Stronger agrochemical and water quality control regulations have also been proposed [66]. However, proper treatment and control of the disease will not be possible without a substantial investment in improving living conditions in the endemic areas and financing research efforts to clarify the causal chain involved in kidney damage.

New therapies for already established MeN, such as intrarenal administration of adipose-derived mesenchymal cells, have been attempted. Preliminary results showed stabilization of the renal function among patients with less advanced stages of CKD.

APOL1-Related CKD As the APOL-1 variant genes present incomplete penetrance, preventive efforts regarding APOL1-related CKD should focus on avoiding the occurrence of contributing factors, such as HIV infection or other disease states associated with high inflammation, especially interferon surges. New strategies aiming at the gene variant itself are under development. The small molecule inaxaplin reverses the toxic gain-of-function effect of APOL-1 high-risk variants. Inaxaplin was tested in a short-term phase 2a study in participants with two APOL1 variants and biopsy-proven FSGS. After 13 weeks of treatment, most participants had a clinically significant reduction in proteinuria [65].

34.6 Future Directions

CKDu is a significant public health issue with important social and economic repercussions for LIC and LMIC. Typically, patients affected by CKDu are young men who are the heads of their households and the family's financial support. These deleterious effects are seen from the household level to the national economy, creating an important burden for the healthcare system. The combined effects of losing the working force and increasing economic expenditures disproportionally preclude the World Health Organization's Sustainable Development Goal (SDGs) of ending poverty and inequality, ensuring that all people enjoy health, justice, and prosperity. Early diagnosis and prevention of CKD progression are crucial to mitigate these effects. Establishing outpatient clinics in rural areas, early screenings for at-risk individuals, and referrals to nephrology specialists are some of the interventions that may reduce the morbidity and mortality of CKDu.

The APOL1-related CKD also affects the sub-Saharan black population and their immigrated descendants, frequently disadvantaged individuals.

To best manage to attain the WHO goals, there are necessary efforts:

1. First, the recognition of CKD by WHO as a major NCD to be targeted further than a consequence of diabetes and hypertension, considering the myriad of CKD causes and even the burden of non-recognized causes in LMIC.
2. Mandatory and patient-centered registries on CKD and KRT must be fostered and funded worldwide to provide complete and reliable data on the disease. We cannot change what we do not know.
3. Funding research on CKDu in its hotspots in Central America and South Asia. Clinical (mainly longitudinal) and epidemiological research is essential to identify causal and risk factors for CKDu in their hotspots.
4. Provide earlier diagnosis methods, including point-of-care glomerular filtration rate estimation, kidney biopsies, and genetic testing.
5. We recommend increased funding and education for primary care physicians in rural areas who can detect early signs of kidney disease in order to prevent CKD. These clinics should be supported to perform appropriate testing, preventative interventions, and timely specialist referrals.
6. Provide specialized care for CKD. Most of the population from the CKDu hotspot in Central America resides in rural areas, where access to health care is a major challenge. There is a lack of specialists in this region (Nicaragua had only 35 nephrologists in 2023).

7. Peritoneal dialysis must be funded, and training on the method and the necessary physical structure of the home must be provided.
8. The diagnostic arsenal for CKD etiologic diagnosis, including kidney biopsies and genetic investigation, should be increasingly available in LIC and LMIC, to reduce the percentage of CKDu.

34.7 Take-Home Message

- KDIGO guidelines recommend not attributing a cause to CKD based only on the presence of comorbidities, such as diabetes and hypertension [6].
- CKD of unknown origin should be admitted and investigated through image and laboratory exams, kidney biopsy, and genetic testing.
- High-risk populations should be screened using point-of-care estimation of the glomerular filtration. A urine dipstick alone is insufficient, considering proteinuria and hematuria are not earlier or ubiquitous manifestations of CKDu.
- Guidelines for preventing, diagnosing, and treating CKDu should be developed to allow for early identification and proper registration.

References

1. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases, Nephrology Dialysis Transplantation, vol. 34. Oxford University Press; 2019. p. 1803–5.
2. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int. 2015;88(5):950–7.
3. Stanifer JW, Jing B, Tolan S, Helmke N, Mukerjee R, Naicker S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(3):e174–81.
4. Stanifer JW, Muiru A, Jafar TH, Patel UD. Chronic kidney disease in low- and middle-income countries, Nephrology Dialysis Transplantation, vol. 31. Oxford University Press; 2016. p. 868–74.
5. Vivante A. Genetics of chronic kidney disease. N Engl J Med [Internet]. 2024;391(7):627–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/39141855
6. Levey AS, Eckardt KU, Dorman NM, Christiansen SL, Hoorn EJ, Ingelfinger JR, et al. Nomenclature for kidney function and disease: report of a kidney disease: improving global outcomes (KDIGO) consensus conference. Kidney Int [Internet]. 2020;97(6):1117–29. Available from: https://doi.org/10.1016/j.kint.2020.02.010.
7. Siewert-Delle A, Ljungman S, Andersson OK, Wilhelmsen L. Nephrology dialysis transplantation does treated primary hypertension lead to end-stage renal disease? A 20-year follow-up of the primary prevention study in Göteborg, Sweden, Nephrol Dial Transplant, vol. 13; 1998.
8. ERA-EDTA Registry. ERA-EDTA registry: annual report 2016. Vol. 80. 2016.
9. ERA-EDTA Registry. ERA-EDTA registry annual report 2019. Amsterdam; 2021.
10. Nerbass FB, Lima H d N, Moura-Neto JA, Lugon JR, Sesso R. Brazilian Dialysis Survey 2022. Braz J Nephrol [Internet]. 2024;46(2) Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0101-28002024000200306&tlng=en.
11. Wijkström J, Jayasumana C, Dassanayake R, Priyawardane N, Godakanda N, Siribaddana S, et al. Morphological and clinical findings in Sri Lankan patients with chronic kidney disease of unknown cause (CKDu): similarities and differences with Mesoamerican Nephropathy. PLoS One. 2018;13(3):e0193056.
12. Ganguli A. Uddanam nephropathy/regional nephropathy in India: preliminary findings and a plea for further research. Am J Kidney Dis. 2016;68(3):344–8.
13. Grollman AP, Shibutani S, Moriya M, Miller F, Wu L, Moll U, et al. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. Proc Natl Acad Sci. 2007;104(29):12129–34.
14. Tsuchiya K. Causation of ouch-ouch disease (Itai-Itai Byo)-an introductory review. Keio J Med. 1969;18(4):195–211.
15. Hoy W, Bs MB, Ordunez P. EpidEmic of chronic Kidney disease in agricultural communities in central america [Internet]. 2017. Available from: www.paho.org
16. Trabanino RG, Aguilar R, Silva CR, Mercado MO, Merino RL. Nefropatía terminal en pacientes de un hospital de referencia en El Salvador. Revista Panamericana de Salud Pública [Internet]. 2002;12(3):202–6. Available from: http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S1020-49892002000900009&lng=es&nrm=iso&tlng=es
17. Torres C, Aragón A, González M, López I, Jakobsson K, Elinder CG, et al. Decreased kidney function of

unknown cause in Nicaragua: a community-based survey. Am J Kidney Dis. 2010;55(3):485–96.
18. Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman DH. Resolving the enigma of the mesoamerican nephropathy: a research workshop summary. Am J Kidney Dis. 2014;63(3):396–404.
19. Ruwanpathirana T, Senanayake S, Gunawardana N, Munasinghe A, Ginige S, Gamage D, et al. Prevalence and risk factors for impaired kidney function in the district of Anuradhapura, Sri Lanka: a cross-sectional population-representative survey in those at risk of chronic kidney disease of unknown aetiology, BMC Public Health, vol. 19. BioMed Central Ltd; 2019.
20. Jayatilake N, Mendis S, Maheepala P, Mehta FR. Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country. BMC Nephrol. 2013;14(1)
21. Herath C, Jayasumana C, De Silva PMCS, De Silva PHC, Siribaddana S, De Broe ME. Kidney diseases in agricultural communities: a case against heat-stress nephropathy. Kidney Int Rep [Internet]. 2018;3(2):271–80. Available from: https://doi.org/10.1016/j.ekir.2017.10.006.
22. Francis A, Harhay MN, Ong ACM, Tummalapalli SL, Ortiz A, Fogo AB, et al. Chronic kidney disease and the global public health agenda: an international consensus. Nat Rev Nephrol [Internet]. 2024;20(July):473–85. Available from: https://doi.org/10.1038/s41581-024-00820-6.
23. Wimalawansa SJ, Dissanayake CB. Factors affecting the environmentally induced, chronic kidney disease of unknown aetiology in dry zonal regions in tropical countries—novel findings, Environments – MDPI, vol. 7. MDPI AG; 2020.
24. Wijewickrama E, Alam MR, Bajpai D, Divyaveer S, Iyengar A, Kumar V, et al. Capacity for the management of kidney failure in the International Society of Nephrology South Asia region: report from the 2023 ISN Global Kidney Health Atlas (ISN-GKHA), Kidney International Supplements, vol. 13. Elsevier B.V; 2024. p. 123–35.
25. Tatapudi RR, Rentala S, Gullipalli P, Komarraju AL, Singh AK, Tatapudi VS, et al. High prevalence of CKD of unknown etiology in Uddanam, India. Kidney Int Rep. 2019;4(3):380–9.
26. Nerli RB, Tanmaya Metgud, Hiremath MB, Guntaka A, Patil S and Prabha V. Prevalence of renal disorders among the residents of Canacona in India: analysis of the data from a free urological medical camp. Indian Journal of Science and Technology 2010; 3(3):296–8.
27. Mohanty NK, Sahoo KC, Pati S, Sahu AK, Mohanty R. Prevalence of chronic kidney disease in Cuttack district of Odisha, India. Int J Environ Res Public Health. 2020;17(2)
28. El Minshawy O. End-stage renal disease in the El-Minia Governorate, upper Egypt: an epidemiological study. Saudi J Kidney Dis Transpl. 2011 Sep;22(5):1048–54.
29. Aguilar DJ, Madero M. Other potential CKD hotspots in the world: the cases of Mexico and the United States. Semin Nephrol. 2019;39(3):300–7.
30. Garcia-Garcia G, Gutiérrez-Padilla A, Perez-Gomez HR, Chavez-Iñiguez JS, Morraz-Mejia EF, Amador-Jimenez MJ, et al. Chronic kidney disease of unknown cause in Mexico: the case of Poncitlan, Jalisco. Clin Nephrol. 2020;93(1):42–8.
31. Villalvazo P, Carriazo S, Martin-Cleary C, Ortiz A. Aguascalientes: one of the hottest chronic kidney disease (CKD) hotspots in Mexico and a CKD of unknown aetiology mystery to be solved, Clinical Kidney Journal, vol. 14. Oxford University Press; 2021. p. 2285–94.
32. Stanifer JW, Jing B, Tolan S, Helmke N, Mukerjee R, Naicker S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health [Internet]. 2014;2(3):e174–81. Available from: https://doi.org/10.1016/S2214-109X(14)70002-6.
33. Fiseha T, Ekong NE, Osborne NJ. Chronic kidney disease of unknown aetiology in Africa: a review of the literature. Nephrology. 2024;29(4):177–87.
34. Ulasi II, Ijoma CK. The enormity of chronic kidney disease in Nigeria: the situation in a teaching hospital in south-east Nigeria. J Trop Med. 2010;
35. Diouf B, Ka EF, Niang A, Diouf ML, Mbengue M, Diop TM. Etiologies of chronic renal insufficiency in an adult internal medicine service in Dakar. Dakar Med [Internet]. 2000;45(1):62–5. Available from: http://europepmc.org/abstract/MED/14666794
36. Desta BZ, Dadi AF, Derseh BT. Mortality in hemodialysis patients in Ethiopia: a retrospective follow – up study in three centers. BMC Nephrol [Internet]. 2023;(January 2022) Available from: https://doi.org/10.1186/s12882-022-03053-6.
37. Elsharif ME, Elsharif EG. Causes of end-stage renal disease in Sudan: a single-center experience. Saudi J Kidney Dis Transplant. 2011;22(2):373–6.
38. Rage HI, Ers SA, Kahin AY, Elmi MM, Mohamed AA, Kumar JP. Causes of kidney failure among patients undergoing maintenance hemodialysis in Somalia: a multi-center study. BMC Nephrol. 2023;24(1):1–6.
39. George JA, Brandenburg JT, Fabian J, Crowther NJ, Alberts M, Ali S, et al. Kidney damage and associated risk factors in rural and urban sub-Saharan Africa (AWI-Gen): a cross-sectional population study. Lancet Glob Health. 2020;7(12)
40. United States Renal Data System. USRDS annual data report: epidemiology of kidney disease in the United States (National Institute of Diabetes and Digestive and Kidney Diseases, 2022). National Institute of Diabetes and Digestive and Kidney Diseases. 2022
41. Reeders ST, Breuning MH, Davies KE, Nicholls RD, Jarman AP, Higgs DR, et al. A highly polymorphic DNA marker linked to adult polycystic kidney disease on chromosome 16. Nature. 1985;317(6037):542–4.

42. Groopman EE, Marasa M, Cameron-Christie S, Petrovski S, Aggarwal VS, Milo-Rasouly H, et al. Diagnostic utility of exome sequencing for kidney disease. N Engl J Med. 2019;380(2):142–51.
43. Mallawaarachchi AC, Fowles L, Wardrop L, Wood A, O'Shea R, Biros E, et al. Genomic testing in patients with kidney failure of an unknown cause: a national Australian study. Clin J Am Soc Nephrol. 2024;19(7):887–97.
44. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science (1979). 2010;329(5993):841–5.
45. Friedman DJ, Pollak MR. Apol1 nephropathy: from genetics to clinical applications. Clin J Am Soc Nephrol. 2021;16(2):294–303.
46. Perez-Gomez MV, Martin-Cleary C, Fernandez-Fernandez B, Ortiz A. Meso-American nephropathy: what we have learned about the potential genetic influence on chronic kidney disease development*. Clin Kidney J. 2018;11(4):491–5.
47. Nanayakkara S, Senevirathna S, Abeysekera T, Chandrajith R, Ratnatunga N, Gunarathne E, et al. An integrative study of the genetic, social and environmental determinants of chronic kidney disease characterized by tubulointerstitial damages in the North Central region of Sri Lanka. J Occup Health. 2014;56(1):28–38.
48. Nanayakkara S, Senevirathna S, Parahitiyawa NB, Abeysekera T, Chandrajith R, Ratnatunga N, et al. Whole-exome sequencing reveals genetic variants associated with chronic kidney disease characterized by tubulointerstitial damages in North Central region, Sri Lanka. Environ Health Prev Med. 2015;20(5):354–9.
49. Glaser J, Lemery J, Rajagopalan B, Diaz HF, García-Trabanino R, Taduri G, et al. Climate change and the emergent epidemic of CKD from heat stress in rural communities: the case for heat stress nephropathy. Clin J Am Soc Nephrol. 2016;11(8):1472–83.
50. Butler-Dawson J, Krisher L, Asensio C, Cruz A, Tenney L, Weitzenkamp D, et al. Risk factors for declines in kidney function in sugarcane workers in Guatemala. J Occup Environ Med. 2018;60(6):548–58.
51. Vervaet BA, Nast CC, Jayasumana C, Schreurs G, Roels F, Herath C, et al. Chronic interstitial nephritis in agricultural communities is a toxin-induced proximal tubular nephropathy. Kidney Int [Internet]. 2020;97(2):350–69. Available from: https://doi.org/10.1016/j.kint.2019.11.009.
52. Jayasumana C, Paranagama P, Agampodi S, Wijewardane C, Gunatilake S, Siribaddana S. Drinking well water and occupational exposure to Herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka. Environ Health. 2015;14(1):6.
53. Jayasumana C, Gunatilake S, Senanayake P. Glyphosate, hard water and nephrotoxic metals: are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in Sri Lanka? Int J Environ Res Public Health. 2014;11(2):2125–47.
54. Riefkohl A, Ramírez-Rubio O, Laws RL, McClean MD, Weiner DE, Kaufman JS, et al. *Leptospira* seropositivity as a risk factor for Mesoamerican Nephropathy. Int J Occup Environ Health. 2017;23(1):1–10.
55. Herrera R, Orantes CM, Almaguer M, Alfonso P, Bayarre HD, et al. Clinical characteristics of chronic kidney disease of nontraditional causes in Salvadoran farming communities. MEDICC Rev. 2014;16(2):39.
56. Fischer RSB, Mandayam S, Chavarria D, Vangala C, Nolan MS, Garcia LL, et al. Clinical evidence of acute Mesoamerican nephropathy. Am J Trop Med Hyg. 2017;97(4):1247–56.
57. Raimann JG, Riella MC, Levin NW. International Society of Nephrology's 0by25 initiative (zero preventable deaths from acute kidney injury by 2025): focus on diagnosis of acute kidney injury in low-income countries. Clin Kidney J. 2018;11(1):12–9.
58. Hench PS. The concentration of urea in saliva. JAMA J Am Med Assoc. 1922;79(17):1409.
59. Akai T, Naka K, Yoshikawa C, Okuda K, Okamoto T, Yamagami S, et al. Salivary urea nitrogen as an index to renal function: a test-strip method. Clin Chem. 1983;29(10):1825–7.
60. Raimann JG, Kirisits W, Gebetsroither E, Carter M, Callegari J, Rosales L, et al. Saliva urea dipstick test: application in chronic kidney disease. Clin Nephrol. 2011;76(07):23–8.
61. Calice-Silva V, Vieira MA, Raimann JG, Carter M, Callegari J, Levin NW, et al. Saliva urea nitrogen dipstick – a novel bedside diagnostic tool for acute kidney injury. Clin Nephrol. 2014;82(12):358–66.
62. Calice-Silva V, Sacomboio E, Raimann JG, Evans R, dos Santos SC, Tchivango AT, et al. Diagnostic performance of salivary urea nitrogen dipstick to detect and monitor acute kidney disease in patients with malaria. Malar J. 2018;17(1):477.
63. Evans R, Calice-Silva V, Raimann JG, Hemmila U, Craik A, Mtekateka M, et al. Diagnostic performance of a Saliva urea nitrogen dipstick to detect kidney disease in Malawi. Kidney Int Rep. 2017;2(2):219–27.
64. Hussein RH, Calice-Silva V, Evans R, Levin NW, Ellidir RA, Ali EM, et al. Diagnosis of acute kidney injury in children hospitalized in a Sub-Saharan African unit by saliva urea nitrogen dipstick test. Blood Purif. 2020;49(1–2):185–96.
65. Egbuna O, Zimmerman B, Manos G, Fortier A, Chirieac MC, Dakin LA, et al. Inaxaplin for proteinuric kidney disease in persons with two APOL1 variants. N Engl J Med. 2023;388(11):969–79.
66. ELi Z, Fantke P. Toward harmonizing global pesticide regulations for surface freshwaters in support of protecting human health. Journal of Environmental Management, 2022;301(11):3909. https://doi.org/10.1016/J.JENVMAN.2021.11390979.

35 Tropical Diseases in Kidney Transplantation

Lucio Requião Moura, Silvana Daher Costa, and Taina Veras de Sandes-Freitas

35.1 Introduction

Infections are the leading cause of death in kidney transplant recipients living in Latin American countries [1, 2]. Data from a Brazilian study including 10,400 kidney transplant recipients from a single center located in the Southeast of the country indicate that 34% of deaths after transplantation were due to infections [2]. Even in developed countries, where cardiovascular events are the leading cause of death after transplantation, infections represent the second or third cause [3–5]. Within the vast universe of infectious diseases that affect these patients, tropical diseases deserve attention due to the increasing number of reports in recent years, their diagnostic and therapeutic peculiarities, and their impact on patient and graft outcomes [6].

The increase in the number of cases reported in the literature is probably a consequence of the growth of transplant programs in low- and middle-income countries, most of which are located in tropical and subtropical regions, such as Brazil, Argentina, Mexico, India, China, and Africa [7, 8]. Other causes include increased survival and quality of life of transplant patients, resulting in greater mobility between regions of the world and exposure to environmental and occupational risks; migration of individuals living in different regions of the world to tropical or subtropical countries; and undesirable transplant tourism [9–12]. Another factor that deserves attention in current times is the impact of climate change on ecological systems involving vectors, given that autochthonous cases of tropical diseases have been detected in countries with cold climates. On the other hand, it is important to highlight that, despite the increasing number of reports, tropical diseases occur predominantly in countries with weaker health services, surveillance, and reporting systems, which results in underdiagnosis and underreporting, besides health access difficulties.

L. Requião Moura
Federal University of São Paulo, São Paulo, SP, Brazil

S. D. Costa
Division of Kidney Transplantation, Walter Cantidio University Hospital, Federal University of Ceará, Fortaleza, Ceará, Brazil

Division of Kidney Transplantation, General Hospital of Fortaleza, Fortaleza, Ceará, Brazil

T. V. de Sandes-Freitas (✉)
Division of Kidney Transplantation, General Hospital of Fortaleza, Fortaleza, Ceará, Brazil

Department of Internal Medicine, School of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2025

G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3_35

35.2 Transmission Routes

Understanding the forms of transmission of tropical diseases after transplantation is essential for implementing preventive measures. Kidney transplant recipients can acquire any of the tropical diseases through direct acquisition in the community, the de novo *form*, as can any other exposed individual. This type of transmission is more frequent after the first year of transplantation, when the patient is fully rehabilitated and carrying out his/her work and social activities. It is a frequent form of acquisition in patients living in tropical countries and in those who acquire the disease while traveling. It is worth noting that immunosuppression used to prevent rejection significantly increases the risk of infections in which cellular immunity plays an important role, such as tuberculosis and leishmaniasis. It is important to emphasize that kidney transplant recipients, in addition to the permanent state of immunosuppression, are individuals more prone to interventions, such as hospitalizations and blood transfusions, which makes them more susceptible to acquiring and developing infections. Chagas disease, leishmaniasis, malaria, and Zika are examples of diseases that can be transmitted via blood transfusion [8, 13, 14].

Another common form is the reactivation or recrudescence of latent diseases, more frequent in the first months after transplantation, resulting from the compromised immune response resulting from high exposure to immunosuppressive agents at this stage. Tuberculosis, disseminated strongyloidiasis, Chagas disease, malaria, and leishmaniasis are examples of this form of acquisition, which predominates in individuals living in endemic areas.

More rarely, the disease can be acquired by transmission from the donor through the transplanted organ. In this case, the disease manifests at any time after the transplant, but usually occurs early, in the first few weeks. Chagas disease, tuberculosis, malaria, leishmaniasis, toxoplasmosis, diseases associated with HTLV-1 and dengue are examples already reported in this modality [9, 11, 15, 16].

35.3 Peculiarities of Clinical Presentation

Diagnosis of certain infections in this population is sometimes more difficult than in immunocompetent patients. The physiological response to infections may be modified by immunosuppressive agents, resulting in atypical clinical picture [17, 18]. For example, eosinophilia is often absent in cases of Strongyloides hyperinfection [19]; granulomas may be absent in cases of tuberculosis and schistosomiasis [18]; fever in malaria may present without the typical cyclical pattern [11, 20]; and cytopenias, notably anemia and thrombocytopenia, are more common in the course of infectious diseases in kidney transplant recipients than in immunocompetent individuals [21]. Some diseases such as malaria, Chagas disease, strongyloidiasis, and measles may have an aggressive clinical presentation and rapid progression to sepsis [9, 11]. Although previous studies have speculated that patients with impaired cellular immunity would be less likely to develop hemorrhagic fever and dengue shock syndrome, since these are presentations with intense inflammatory activity and release of T lymphocyte-dependent cytokines [8, 16], a more recent systematic review reported a higher incidence of severe dengue and higher mortality among transplant recipients [22].

Understanding these diagnostic challenges is essential to guide investigation, which must be agile and often based on invasive diagnostic tests, such as biopsies, and costly tests, such as serological tests, molecular biology, and cultures. As for diagnostic tests, those that depend on antibody detection, such as serology, may be false-negative or become positive late. Skin tests that depend on delayed hypersensitivity, such as the Montenegro test, used to diagnose leishmaniasis, and the Mantoux reaction, which is the PPD (*purified protein derivative)* tuberculous test, are also frequently negative. In this context of anergy, *interferon-gamma release* assays (IGRA*)* have emerged as interesting alternatives [23, 24]. In situations of high clinical suspicion and impossibility of diagnostic conclusion, empirical treatment is often justified, especially in endemic

countries [25, 26]. The association of tropical diseases in kidney transplant recipients with other infectious diseases, such as bacteria, cytomegalovirus, and *Epstein–Baar* virus, is frequent [27, 28], not always symptomatic and probably indicative of an exacerbated state of immunosuppression.

In addition to the signs and symptoms related to the tropical disease, impairment of kidney graft function is common at diagnosis and throughout the treatment period. The main reasons are hypovolemia, dehydration, sepsis, nephrotoxicity due to contrast agents used in diagnostic tests, nephrotoxicity of therapeutic agents, inflammatory and fibrotic activity of urinary tract infection, such as that which occurs in renal tuberculosis, or other urological complications, such as schistosomiasis, rhabdomyolysis in leptospirosis, in addition to specific lesions resulting from the direct action of infectious agents or immune complexes, such as those observed in acute interstitial nephritis in leptospirosis or leishmaniasis, glomerulonephritis associated with schistosomiasis, leishmaniasis, and malaria [25, 29–32].

35.4 Interference of Immunosuppressive Drugs

The immune response to parasitic infections is relatively more preserved than the response to viral and bacterial infections, since immunosuppressive drugs are predominantly aimed at suppressing T cells, with less action on macrophages and, mainly, on eosinophils [11]. On the other hand, tropical diseases whose immune response is predominantly cellular and dependent on the action of T lymphocytes, such as tuberculosis, have a notably higher incidence after transplantation [33].

In addition to the generic action of inhibiting the innate and adaptive immune response, some immunosuppressive agents have been specifically associated with certain infections. Previous studies have associated the use of inhibitors of the *mammalian target of rapamycin* (mTOR) to an increased risk of developing tuberculosis [34, 35]. In addition to inhibiting cellular immunity, mTOR inhibitors stimulate the production of interleukin-10, facilitating the reactivation of latent infections. In contrast, studies indicate that sirolimus and temsirolimus, examples of mTOR inhibitors, can induce the degradation of Koch's bacillus [36]. Recent studies have described high incidences of tuberculosis in kidney transplant recipients using belatacept, but the mechanism by which this drug can favor the emergence of the disease, other than blocking the activation and proliferation of T lymphocytes, is not clear [26, 37].

Steroids are attributed a direct effect on *Strongyloides stercolaris*, accelerating the transformation of the rhabditiform larva into the filariform larva, as well as favoring the reproduction of adult females, which results in a greater risk of hyperinfection [38]. On the other hand, through uncertain mechanisms, cyclosporine appears to have antiparasitic actions. Previous studies have associated its use with a lower incidence of malaria, strongyloidiasis and Chagas disease [38–41]. There is also evidence that points to the effect of inhibiting the viral replication of flaviviruses by competing for binding with cyclophilin [42].

35.5 Peculiarities in Treatment

Kidney graft function is commonly affected during the treatment of certain infections. Among the main reasons is the nephrotoxicity of drugs, such as amphotericin B, used in the treatment of leishmaniasis and fungal infections. In addition, interactions between drugs used in the treatment of tropical diseases and immunosuppressive agents are not uncommon, causing an increase or decrease in the exposure of these agents, which can result in nephrotoxicity or rejection, respectively. As examples, azole derivatives, such as ketoconazole, fluconazole, itraconazole, and voriconazole, used in the treatment of fungal infections, are potent inhibitors of cytochrome P450, resulting in increased exposure to calcineurin inhibitors, mTOR inhibitors, and prednisone. In contrast, rifampicin, used in the treatment

of tuberculosis and leprosy, is a potent inducer of cytochrome P450 (CYP 3A4), resulting in reduced exposure to these drugs [43, 44]. In this context, there is a need for frequent adjustments of immunosuppressant doses, as well as more frequent monitoring of their blood levels.

Patients with impaired kidney function may require modifications to standard treatment or dose adjustments. The duration of treatment for tropical diseases in immunosuppressed patients is also a subject of debate. For example, several centers choose to extend tuberculosis treatment for up to 18 months in transplant recipients, with the aim of ensuring eradication of the disease and reducing the reactivation rate [45].

Another important aspect is the management of immunosuppression during infection. Given that the cellular immune response is essential for the resolution of these diseases, reducing the doses and concentrations of immunosuppressive drugs is often necessary, especially in severe patients [46]. However, patients underexposed to immunosuppression are more susceptible to immune-mediated events, such as acute and chronic rejection [11]. Thus, there is no evidence to support a universal recommendation in these cases and the decision must be individualized.

35.6 Impact on the Patient and Kidney Graft

In general, tropical diseases present higher morbidity and mortality in immunosuppressed patients. Better outcomes are observed when diagnosis and treatment are early instituted. In addition to the negative outcomes in patient survival, evidence points to a negative impact on kidney graft, with irreversible impairment of kidney function and even graft loss [25].

35.7 Aspects of Prevention in the Transplant Recipient Population

The strategies for preventing infectious diseases in kidney transplantation can be didactically understood under three aspects: prevention of transmission by the donor; reactivation of latent infections present in the recipient before the transplant; and those acquired in the community, or so-called de novo *infections*.

In the evaluation of the recipient, two strategies should be used before the transplant: a minimum *screening* for certain infectious diseases and updating the vaccination schedule. According to the Brazilian guidelines for the care of patients with chronic kidney disease, all patients should be referred to an immunization center to update their vaccination schedule, as early as they are in conservative treatment [47]. Table 35.1 describes the main vaccines and the possibility of their use before and after the transplant, in accordance with the recommendations of the American Centers for Disease Control and Prevention (CDC) and referenced by the Brazilian Association of Organ Transplants–ABTO [48, 49].

The purpose of pretransplant infectious disease screening is to identify conditions that exclude recipients, identify and treat active infection, determine the risk of infection, and define strategies for infection prevention after transplantation. Brazilian transplant legislation, through ordinance 2600 of the Ministry of Health, determines that all candidates for kidney transplantation must undergo at least the following serologies: HIV, Human T-lymphotropic virus (HTLV) I and II, AgHBs, total AntiHBc, Anti-HCV, immunofluorescence for Chagas disease, IgG and IgM for Cytomegalovirus (CMV) and EBV, Venereal Disease Research Laboratory (VDRL), and immunofluorescence for lues [50]. In addition to these tests, it is suggested that serology be performed for toxoplasmosis, as well as the AntiHBs test [51]. Below, we will discuss some of the most relevant strategies that should be considered in the care of kidney recipients in Brazil.

Given this mandatory minimum screening, two situations may be encountered and deserve to be highlighted in the context of tropical infectious diseases: Chagas disease and HTLV infection. Chagas disease will be addressed later in this chapter, including its prophylactic strategies. HTLV serology must be performed for kidney recipients and donors. Seropositive donors must be excluded. Seroprevalence varies depending on the population studied, being

Table 35.1 Vaccines indicated according to the stage of the transplant

Vaccine	Type	Pre-Tx	Post-Tx	Donors	Contacts
Covid-19	I	Yes	Yes	Yes	Yes
Dengue[a]	GO	A.D	No	Yes	Yes
Diphtheria/tetanus (dT)	I	Yes	Yes	Yes	Yes
Diphtheria/tetanus/pertussis (dTpa)	I	Yes	Yes	Yes	Yes
Yellow fever[b]	GO	Yes	No	Yes[c]	Yes[c]
Haemophilus influenzae b (Hib)	I	Yes	Yes	Yes[c]	Yes[c]
Shingles[d]	I	Yes	Yes	Yes[c]	Yes[c]
HPV[e]	I	Yes	Yes	Yes[c]	Yes[c]
Hepatitis A[f]	I	Yes	Yes	Yes[c]	Yes[c]
Hepatitis B[f]	I	Yes	Yes	Yes[c]	Yes[c]
Influenza (Flu)[g]	I	Yes	Yes	Yes	Yes
Meningococcus[h]	I	Yes	Yes	Yes[c]	Yes[c]
Pneumococcus[i]	I	Yes	Yes	Yes[c]	Yes[c]
Oral polio[j]	GO	No	No	No	No
Inactivated polio[j]	I	Yes	Yes	Yes[c]	Yes[c]
Anger[k]	I	Yes	Yes	Yes[c]	Yes[c]
Measles/mumps/rubella (MMR)[i]	GO	Yes	No	Yes	Yes
Chickenpox[l]	GO	Yes	No	Yes	Yes
Respiratory syncytial virus (RSV)[m]	I	Yes	Yes	Yes[c]	Yes[c]

Adapted from "PRE and POST-ADULT ORGAN TRANSPLANT VACCINATION—2024" by the Transplant Infection Commission (COINT) Brazilian Organ Transplant Association (ABTO)
Pre-Tx—use indicated in the pretransplant phase; Post-Tx—use indicated in the posttransplant phase; Donors—use indicated for donors; Contacts—use indicated for home contacts and healthcare team
VA live attenuated virus, *I* inactivated, fragmented or recombinant microorganism, *DC* shared decision
[a] Approved by ANVISA and recommended by the Brazilian Society of Immunizations for all immunocompetent individuals aged 4–60 years. There is no evidence of safety in patients with chronic kidney disease. The ABTO Transplant Infection Committee (COINT) guides shared decision-making between the medical team and the patient
[b] Indicated pretransplant. Wait 3 weeks before transplanting
[c] Indicated in the routine of each calendar and not specifically for being a donor and/or cohabitant
[d] Over 18 years old
[e] Up to 45 years old in the public network and no age limit in the private network
[f] For individuals with negative serology
[g] Vaccinate annually in the fall
[h] Meningococcus C or tetravalent Meningococcus (A,C,W,Y): Approved for children and adults and available in the public network; Meningococcus B: Approved for children and adults and only available through supplementary healthcare
[i] Pneumo 13: Approved for children and adults and available on the public network; Pneumo15/Pneumo20: Approved for children and adults and only available through supplementary healthcare; Pneumo 23: Available in the public network for patients with chronic kidney disease pre- and posttransplant
[j] Only individuals not previously vaccinated or with an incomplete vaccination schedule
[k] In special risk situations. If post-exposure in transplant patients, associate immunoglobulin
[l] For individuals with no prior history of disease or individuals not previously vaccinated or with incomplete vaccination schedule.
[m] Approved for adults over 60 years of age, single dose and only available through supplementary healthcare

as low as 0.13% in the north of the country, to over 1% in Bahia [52, 53]. In American studies, positive serology in potential donors reached levels as high as 2.2–4.4% [54, 55]. HTLV infection causes tropical spastic paralysis, neurogenic bladder, and T-cell lymphoma, the latter being uncommon after kidney transplantation. There is no defined strategy for monitoring transplantation in seropositive recipients, but the risk of reactivation should be considered as a potential contraindication to transplantation. There is no standardized recommendation for recipients inadvertently infected through graft transmission, but there are reports of the use of antiretroviral strategies after transplantation [56].

Tuberculosis is a common concern in endemic areas such as Brazil. Chest radiography should be performed on all candidates to identify the primary complex. The intradermal PPD test may be useful in non-endemic areas, but most patients with tuberculosis after transplantation are anergic in the pretransplant period. More recently, tests that evaluate the specific cellular response to the agent through measurements of interferon-gamma production, such as IGRAs, have gained importance [57]. Since BCG vaccination is mandatory in Brazil, virtually all candidates were vaccinated, but it is important to look for evidence of vaccination on physical examination, identified by the characteristic scar in the deltoid region. The risk of transmission by the donor has been estimated at 30%, therefore organs from donors with known active infection should be disregarded [58, 59]. Prophylaxis for recipients at high risk of reactivation, or who have a history of household contact with a recently diagnosed patient, or with donors with a recent history of infection should be administered with isoniazid 300 mg/day for 6–9 months after transplantation [60]. The most recent recommendations have also suggested this strategy for recipients with positive PPD or IGRA. Prevention strategies for latent tuberculosis reactivation (LTBI) and the risk of graft transmission will be described in the specific section on tuberculosis later in this chapter.

Another endemic situation in Brazil that requires a well-defined prophylaxis strategy is strongyloidiasis. In general, all kidney transplant recipients should receive prophylaxis, preferably with ivermectin, and may also be administered with albendazole or thiabendazole, 2 weeks before the transplant in cases of living donors, or immediately after the transplant in any case, as well as after intensification of immunosuppression [61, 62]. All transplant recipients should be reinforced with hygiene and self-care measures, which reduce the risk of *reinfection*.

Arboviruses have received special attention due to the high incidence of dengue and previous outbreaks of chikungunya and zika. There are no specific recommendations for prophylaxis in the transplant population. Universal measures, such as mosquito control and use of repellents, are preventive strategies that should be adopted. There is no vaccine for chikungunya and zika. A dengue vaccine was recently approved in Brazil that protects against four serotypes and is indicated for immunocompetent individuals between 4 and 60 years of age, regardless of previous exposure to the disease. However, this is an attenuated virus vaccine, and is contraindicated for immunosuppressed patients, and does not provide safety and efficacy data in individuals with chronic diseases, such as chronic kidney disease. If donor or recipient candidates have received the vaccine, the transplant should be postponed for 30 days [63].

Finally, other endemic situations in certain regions of Brazil deserve to be commented on, such as leishmaniasis and malaria, both due to the presence of recipients residing in these regions and those who need to travel to these areas, and, therefore, prevention strategies for both must be defined.

The risks of leishmaniasis transmission through kidney grafts are not well known [59, 64]. However, donors from endemic areas who are known to be infected should not be used. If there is no evidence of active infection, careful epidemiological and clinical investigations should be carried out on donors living in these regions, and their recipients should be carefully monitored for symptoms or signs of the disease after transplantation [46]. Serology is not frequently used for kidney transplant candidates, but this strategy may be interesting for individuals from areas with high case rates. In recipients with a history of treated infection, symptoms and signs of reactivation should be constantly investigated. Recurrence rates of 20–30% have been reported, so secondary prophylaxis with weekly doses of amphotericin B, monthly doses of antimoniate, or daily doses of fluconazole may be used, especially in the first year after transplantation, although there is no clear evidence for these suggestions [64, 65]. Healthy recipients planning to travel to endemic areas should be advised to use insect repellents, avoid exposing areas of the body by wearing protective clothing, use bed nets, and avoid outdoor activities, particularly in the late afternoon.

Regarding malaria, candidates for donation with active infection should be excluded. In suspected cases, diagnostic confirmation with a blood smear or detection of *Plasmodium DNA or RNA* through PCR (*polymerase chain reaction*) can be used [59]. Recipients from endemic areas, or who received grafts from donors from endemic areas, should be monitored for the presence of symptoms or signs of infection, in addition to characteristic laboratory alterations, especially in the first 2 months after transplantation. *Plasmodium* testing by PCR may eventually be indicated. Healthy recipients who plan to travel to endemic areas should follow the guidelines for avoiding contact with mosquitoes, as described for other diseases transmitted by insect vectors. The use of chemoprophylaxis, which can be performed with doxycycline, chloroquine or atovaquone, should be considered [66].

35.8 Peculiarities of Some Tropical Diseases in Kidney Transplantation

The following section will address the peculiarities of some of the most relevant tropical diseases after kidney transplantation: tuberculosis, leishmaniasis, Chagas disease, arboviruses, and strongyloidiasis.

35.8.1 Tuberculosis

The risk of tuberculosis after organ transplantation is approximately 20–50 times higher than in the general population, even in high income countries [8]. Brazilian studies report tuberculosis incidences of 1–5%. after kidney transplantation, while the incidence rate in the general population is currently 32 cases per 100,000 inhabitants [25, 44, 67]. The disease can be acquired in the three ways mentioned above, with the most common forms in our environment being the reactivation of latent tuberculosis (LTBI), followed by community acquisition and, more rarely, transmission via donor [68].

Tuberculosis after transplantation can be a diagnostic challenge and should always be part of the differential diagnosis of fever without a defined focus. There is often no involvement of the respiratory tract and extrapulmonary forms are predominant in most of the cohorts described. The use of molecular tests (Xpert® MTB/RIF) is an interesting option for the diagnosis of extrapulmonary forms in this population [24]. In the face of clinical deterioration, high suspicion, and impossibility of diagnostic conclusion, empirical treatment has been used in centers located in endemic regions [25, 26].

Treatment of active tuberculosis after transplantation in Brazil follows the recommendations for the general population, with the COXIP-4 regimen (isoniazid, rifampicin, pyrazinamide, ethambutol). The patient should be monitored more frequently, since there is a high risk of hepatotoxicity and drug interactions, especially between rifampicin, a strong inducer of the cytochrome P450 system, and calcineurin inhibitors. In some regions of the world, regimens without rifampicin are proposed for patients with localized disease and without severity criteria. The ideal treatment duration is unclear. Experts recommend extending treatment to 9 months, and several centers around the world maintain the regimen for 12 months. If the patient receives a regimen without rifampicin, even longer treatments, up to 18 months, have been described [43–45, 60].

Treatment of LTBI should be performed with isoniazid (INH) 300 mg/day for 6–9 months, associated with pyridoxine 25–50 mg/day, if possible before transplantation. The great challenge is to identify patients with LTBI, especially in regions of high prevalence, such as Brazil. Treatment is recommended in patients with a previous history of inadequately treated active tuberculosis, close contacts of patients with tuberculosis, in those with radiological images suggestive of untreated tuberculosis, and patients with a positive screening test (PPD $\geq$ 5 mm). However, given the anergy of the cellular immune response of patients with chronic kidney disease, the percentage of false-negative results to PPD is high. It is not clear in this population what the

role of assessing the *booster effect* is, administering an additional dose of tuberculin 7–14 days after the first negative test. In this context, IGRA assays have emerged as an additional tool, improving the sensitivity of screening in this population. Recent guidelines recommend that, if available, patients being evaluated for transplantation in regions of high endemicity should undergo both tests in order to maximize screening sensitivity [43, 44, 60].

Prevention of graft-transmitted tuberculosis should be done by screening for active disease and LTBI in the donor, through clinical and epidemiological history, chest radiography, and PPD and/or IGRA, the latter restricted to the living donor candidate. Transplant recipients whose donors have a history of active tuberculosis or untreated or inadequately treated LTBI should receive isoniazid. Active tuberculosis in the living or deceased donor contraindicates donation. Living donor candidates with LTBI should be treated before donation. Recipients of renal transplants from deceased donors with LTBI should receive isoniazid [44].

35.8.2 Leishmaniasis

Cellular immune response is essential in infection by Leishmania species, and the minority of immunocompetent individuals who come into contact with this protozoan become symptomatic. The impairment of the cellular immune response in immunosuppressed patients favors the emergence of clinical forms: visceral, cutaneous, and mucocutaneous leishmaniasis, the latter two rarely reported in this population [46, 69]. Despite the greater risk of developing clinical disease, it is not possible to state the impact of transplantation on the incidence of leishmaniasis, since this is an uncommon zoonosis, even in endemic areas, such as Brazil. Most Brazilian studies on leishmaniasis after transplantation report case series and are limited to a few regions, making it impossible to draw conclusions about incidence [28, 70–72].

Transmission may occur by infection through a vector, i.e., de novo *acquisition*, reactivation of latent infection and, more rarely, through the transplanted organ or blood transfusion [46, 59]. Most reported cases of leishmaniasis after transplantation are of the visceral form, known as kala-azar, but clinical atypia is described, with a lower frequency of the classic triad consisting of fever, visceromegaly, and cytopenia. A higher incidence of dissemination to other organs and tissues, such as the intestine, oral cavity, lung, and skin, has also been described [28]. Cutaneous and mucocutaneous forms are uncommon after transplantation and there are reports of atypical clinical presentation, with parasitic dissemination resulting in multiple cutaneous lesions, in addition to clinical polymorphism and visceralization. Post-kala-azar dermal leishmaniasis is more common in these patients [64]. The diagnosis follows the same pattern for immunocompetent patients. As mentioned previously, the Montenegro skin test has limited value in anergic patients. Recent studies have demonstrated the use of IGRA for the diagnosis of leishmaniasis in patients on immunosuppression [23].

Given the increased risk of recurrence, the treatment of choice for visceral leishmaniasis in kidney transplant recipients is amphotericin B, preferably the liposomal formulation, given the risk of nephrotoxicity with amphotericin B deoxycholate. Pentavalent antimonials are considered second-line options [64, 69].

35.8.3 Chagas Disease

Among the tropical diseases caused by protozoa, the one that causes the most clinically severe disease in transplant recipients is Chagas disease, caused by *Trypanosoma cruzi*, which is more relevant in heart transplants than in kidney transplants [61]. From a clinical point of view, infection by *T. cruzi* is divided into two phases: acute and chronic. The acute form occurs after vector transmission in endemic regions and is characterized by parasitemia, which is generally asymptomatic, and by a lesion at the site of the vector bite, known as chagoma [73]. There are reports of acute contamination through the ingestion of high parasite loads through the consump-

tion of unpasteurized foods from endemic areas, such as acai derivatives in Brazil [74]. Another form of acute infection is transmission through inadvertent use of infected donors. In endemic cases, after the acute phase and in the absence of treatment, the infection progresses to the chronic phase, characterized by low viremia, and the patient may remain asymptomatic, which characterizes the indeterminate form, or progress to clinically manifested forms, with cardiac or gastrointestinal involvement or other rarer presentations [73, 75].

In solid organ transplantation, three distinct patterns of infection are observed: primary infection, in which there is transmission through the graft donor with positive serology to recipient with negative serology; reactivation in recipients with latent infection, that is, those who present the undetermined form before the transplant; and de novo *infection*, which can occur in residents of endemic areas, in recipients who have traveled to these areas, or more rarely through transfusion of contaminated blood products, or ingestion of food, as described above [76, 77].

The prevalence of chronic infection in the Brazilian population is estimated at 1.3% [78], and serology testing is mandatory for potential organ donors in the country. The decision to accept a kidney from a donor chronically infected with Chagas disease should take into account that the risk of transmission can reach 10–20% [76, 77, 79]. However, adequate screening for viremia and preemptive treatment minimizes this risk. In Brazil, in a study that evaluated nine transplants performed with seropositive donors, during prophylaxis, no infection was observed in the recipient after the transplant [80]. Likewise, the policy of control and *screening* of blood donors has made transmission by blood products virtually impossible, with a risk of less than 1 for every 200,000 units of products used [81].

In regions where kidney transplantation with seropositive donors is performed, rigorous laboratory monitoring and clinical surveillance are necessary, with PCR being the method of choice. Blood culture and xenodiagnosis are less sensitive and have a long response time, making timely detection of parasitemia difficult [76, 77, 82]. In locations where PCR is not available, surveillance should be performed by direct identification of parasites in the blood using blood smears or, preferably, microhematocrit or the Strout test. A suggested monitoring schedule, based on heart transplantation, is as follows: weekly for the first 2 months, biweekly between the third and sixth months, monthly until the second year, and at any time after intensification of immunosuppression. Preventive treatment is indicated if parasite load is detected, but there is no standardized threshold for initiating treatment in asymptomatic recipients. Regardless of whether reactivation occurs, testing should be performed weekly during treatment until two negative results are obtained. There are few reports describing the use of routine benznidazole prophylaxis for kidney transplant recipients from seropositive donors without parasitemia monitoring [80, 83].

When it occurs, the infection transmitted by the graft is extremely serious, difficult to diagnose, and has a high fatality rate. At autopsy, systemic involvement is generally observed, mainly of the heart, central nervous system, and lungs [61].

A major challenge is the management of recipients carrying the latent or undetermined form. The risk of reactivation is high, with rates of 8–22% reported in kidney transplant recipients [77, 82] and 30–90% in heart transplant recipients [82, 84, 85]. To prevent reactivation, parasitemia should be investigated periodically after transplantation: weekly in the first 2 months, every 2 weeks between the third and sixth months, monthly until the second year, or at any other time after intensification of immunosuppression [59, 86]. Parasitemia can be detected by blood culture, xenodiagnosis, or, preferably, by PCR [59, 61, 82]. Once identified, preemptive treatment should be instituted [58, 59]. Reactivation may manifest as asymptomatic transient parasitemia, skin lesions, myocarditis, and, rarely, systemic.

There is no consistent data on the interference of the type of immunosuppression and the risk of reactivation. In some studies, in heart transplantation, the use of azathioprine was associated with a lower risk of reactivation than mycophe-

nolate [87, 88]. mTOR inhibitors inhibit the growth of the parasite in vitro, suggesting that this class may be a better alternative, but there are no clinical studies exploring this effect [89].

Current treatment is based on two drugs, benznidazole and nifurtimox. Benznidazole is the drug of choice and should be used for a period of at least 2 months [59, 61, 90]. Both drugs are metabolized by cytochrome P450 and may increase blood levels of calcineurin inhibitors, which should be monitored more frequently.

35.8.4 Arboviruses: Dengue, Chikungunya, and Zika

The increase in the incidence of arboviruses dengue, chikungunya, and zika has raised concerns regarding potential complications in patients undergoing kidney transplantation. In general, clinical manifestations are similar to those of the non-transplant population, such as fever, myalgia, nausea, liver enzyme changes, leukopenia, and thrombocytopenia. It is widely known that the main form of transmission is through the bite of the *Aedes aegypti* or *Aedes albopictus* mosquito, however, cases of transmission through blood products and transplanted organs have been reported. The epidemiological context should be considered to assess the risk of nonvector transmission. In a study conducted in Colombia with viral RNA research in blood donation candidates, significantly higher frequencies of positivity for dengue (14.5 vs. 1.9%), chikungunya (8.0 vs. 3.3%), and zika (7.8 vs. 0.3%) were observed in epidemic periods, compared with endemic periods [91].

There is no specific treatment for arboviruses, only supportive measures are implemented. Therefore, preventive strategies are essential and do not differ from those indicated for the general population, as discussed previously. Despite the scarcity of information on arboviruses in transplant recipients, aspects related to dengue, chikungunya, and zika will be discussed below, focusing on this population.

35.8.4.1 Dengue

Dengue fever can be caused by four serotypes of the virus, DENV-1, DENV-2, DENV-3, and DENV-4, and infection by one serotype does not provide immunity against the others. According to some estimates, including those by the World Health Organization (WHO), half of the world's population lives in areas at risk of dengue fever, with approximately 100 million symptomatic cases, 2 million cases of severe disease, and 21 thousand deaths per year [92, 93]. Transmission through blood products or transplanted organs is not common. After infection, viremia lasts approximately 7 days and coincides with the febrile period, during which organ donation is contraindicated. In recent years, the number of cases reported among transplant recipients has increased, however, this should not reflect a specific situation for this group of patients, as this condition is possibly underdiagnosed, given that most cases are asymptomatic [94–96].

Symptomatic infections range from mild, flu-like symptoms to severe symptoms such as hemorrhagic fever and dengue shock syndrome [8]. From a clinical standpoint, there is no reason to consider the disease's evolutionary phases differently from those observed in any host, which are typically recognized as three: the febrile phase, the critical phase, and convalescence [97, 98]. In the first phase, in addition to fever, headache, vomiting, and muscle pain are present, and abdominal pain and diarrhea may occur. During this phase, the leukocyte count decreases, which theoretically may be more pronounced in kidney transplant recipients due to the use of antiproliferatives. After this period, patients who develop more severe symptoms usually present clinical deterioration in 2–5 days, which may occur even after the fever has improved. The critical phase is marked by plasma leakage with consequent hypovolemic shock. Respiratory failure, signs of hepatitis and, classically, an increase in hematocrit and a drop in platelets may occur. Finally, the convalescence phase marks the improvement of the disease, but in sporadic cases, serious changes may occur, such as encephalitis and myocarditis [97].

In 2009, the WHO improved the classification of dengue according to its severity, which helps

health systems and care units in decision-making. This classification is easy to understand, has high sensitivity and high discriminatory power to identify patients with potential progression to more severe conditions [99, 100]. To date, there is no classification system or risk prediction tool specific to kidney transplant recipients and, therefore, the 2009 WHO classification can be applied to diagnosed or suspected cases in this population. Therefore, the presence of the following warning signs should be identified: abdominal pain, persistent vomiting, signs of fluid accumulation, mucosal bleeding, lethargy, liver enlargement of >2 cm, and increased hematocrit level accompanied by reduced platelet count. Patients who present one of the warning signs should be placed under clinical surveillance due to the risk of developing severe dengue fever, which is characterized by evidence of plasma extravasation with consequent dengue shock syndrome, severe bleeding, and organic changes such as hepatitis.

For a long time, it was considered that severe forms would not be more frequent in transplant recipients due to the impairment of cellular immunity, secondary to immunosuppression. However, a systematic review that compared data from 168 kidney transplant recipients included in 11 studies with more than 81 thousand people from the general population demonstrated that the frequency of pleural effusion (17 vs. 2%), ascites (35 vs. 1%), and more severe spectra of dengue (16 vs. 4%) were significantly more frequent among transplant recipients [22].

Patients undergoing transplantation during the incubation period may be at greater risk of severe forms, with the presence of coagulation disorders, which may progress to graft loss and death [95, 101]. However, the descriptions that led to this speculation did not investigate in depth other markers of severity, such as previous infection by a divergent serotype. This is because patients who have already had dengue fever in the past are at greater risk of developing severe forms in the event of new infections by other serotypes. During the infection, there is no consensus on whether immunosuppression should be reduced, as there is no evidence that this approach alters the progression of the disease, in addition to potentially predisposing to rejection [94]. In some practical situations, however, reducing azathioprine or mycophenolate may be necessary in the event of severe leukopenia or thrombocytopenia. Patients receiving cyclosporine have been reported to have milder disease, which may be explained by potential inhibition of flavivirus replication [42, 94].

Viremia can be detected 24–48 h before the onset of fever and persists for 5–6 days, and can be detected through RNA testing by PCR or NS1 protein by ELISA or immunochromatography [102]. The gold standard for diagnosis is PCR, but its unavailability in many centers makes it unviable as a public health measure. The NS1 glycoprotein is correlated with the period of viremia and severity, being detected 9 days after the onset of symptoms and persisting for approximately 18 days [103]. Positive IgM serology appears 3–5 days after the onset of symptoms and remains positive for 3– 6 months and can be used for diagnosis in routine practice, especially in association with NS1 detection in rapid immunochromatographic tests [97]. The association of high IgG titers and low IgM titers suggests previous infection by another serotype. As described above, treatment is limited to support, which varies according to the severity of the clinical manifestation, with no specific therapy.

There are cases of donor-transmission described, although epidemiological investigation presents great challenges. Cases have already been reported in India, Singapore, Colombia, and even France [104–107]. During the 2023–2024 epidemic in Brazil, the Brazilian Association of Organ Transplantation convened a panel of experts who suggested screening for recipients and donors, as summarized in Table 35.2.

35.8.4.2 Chikungunya

Chikungunya fever dates back to 1952, in Tanzania [108]. In 2013, it emerged in Central America and in 2014, the first cases were reported in Brazil [109]. In the last decade, more than 3.6 million cases have been reported in the Americas, 1.6 million of which occurred in Brazil, which is considered the epicenter of the disease [110].

Table 35.2 Recommendations from the Brazilian Transplant Association for donor and recipient screening during the 2024 epidemic

Situation	NS1 positive	IgM positive
Living donor recipient	Wait 30 days after the onset of symptoms to transplant	Postpone the transplant and repeat the serology in 15 days. If IgG is positive, the dengue diagnosis is confirmed, and it is recommended to wait at least 30 days. If IgG is negative, it may be a false positive IgM, and the team will decide whether to proceed with the transplant
Deceased donor recipient	Wait 30 days after the onset of symptoms to transplant	The team must evaluate each case individually. It is recommended to postpone the transplant
Living donor	Do not donate. Wait 30 days after the onset of symptoms to donate	Postpone the transplant
Deceased donor	Delete for donation	IgM may be false negative. The transplant team will continue to assess the situation, considering the endemic situation

Adapted from: de Castro Lima Santos et al. [63]
IgG IgG-type antibody against dengue, *IgM* IgM-type antibody against dengue, *NS1* NS1 antigen for dengue diagnosis

Viremia can last up to 3 weeks after the mosquito bite, with the maximum viral load detected 2 days before the onset of symptoms, persisting for approximately 19 days. Transmission through the transplanted organ is possible, and special vigilance should be exercised in epidemic outbreaks. It is recommended that donors not be accepted until 30 days after the end of symptoms [111].

Unlike Zika and dengue, it is estimated that 85% of patients present symptomatic infection. A recent study showed that immunosuppressed patients using corticosteroids presented less severe symptoms, making it difficult to determine the real incidence of infection in these individuals, even if they live in endemic areas [112, 113]. Symptoms begin with low-grade fever and rash, progressing to headache, myalgia, and arthralgia, which can be debilitating, evolving into a chronic phase lasting months to years in up to half of cases [114, 115]. In general, arthralgia is symmetrical, most frequently affecting large joints. In regions where chikungunya is present, debilitating polyarthralgia has a predictive value greater than 80% for the diagnosis of the disease [116]. In immunosuppressed patients, the intensity of joint symptoms may be milder or absent, and regression of joint complaints after a short period of acute phase may be common [112, 117]. In an Indian study, for example, which compared 44 kidney transplant recipients with 34 non-transplant patients, all with a confirmed diagnosis of chikungunya, there was a significantly lower frequency of musculoskeletal symptoms among the transplant recipients, and the symptoms reported after 3 months were considered minor [118]. On the other hand, in a series of cases diagnosed between 2016 and 2017 in the state of Ceará, all kidney transplant recipients presented arthralgia, approximately half with signs of arthritis, and 44% progressed to a chronic phase of joint symptoms [119]. It is interesting to note that in both series, the frequency of acute kidney injury was approximately 20%.

Laboratory diagnosis depends on the stage of the disease. In the first week, when viremia occurs, the test of choice is PCR, but in transplant patients, viremia is estimated to be shorter, and it is recommended that the diagnostic test be performed in the first days of symptoms [120]. Around the fifth day, IgM becomes positive and may persist for several months. IgG positivity may last for years. Viral isolation is the gold standard, but it is difficult to perform. In general, treatment is limited to symptom management. The effect of immunotherapy and in vitro antiviral activity with the use of favipiravir and ribavirin associated with interferon has been demonstrated in animal models, but these strategies still require proof of efficacy and safety through clinical studies [121–123].

35.8.4.3 Zika

In Brazil, the first confirmed case of Zika was in 2015 [124]. In addition to mosquito bites,

transmission can occur sexually, perinatally, and through blood transfusions [14]. There are still no reports of transmission through transplanted organs. Viremia lasts approximately 7–10 days. Recent studies have shown that viruria is more intense and prolonged than viremia [125]. The National Health Surveillance Agency (ANVISA) recommends waiting at least 30 days after resolution of the condition or after sexual contact with a partner suspected of infection before donating cells, organs, and tissues [126, 127]. In transplants with a living donor, however, when the donor has a recognized infection, it is suggested to wait at least 120 days after the resolution of the condition to make the donation.

There are few reports of the disease in transplant patients, which may be underdiagnosed, given the potential for asymptomatic progression. It is widely known that Zika may be associated with neonatal microcephaly, neurological complications and Guillain-Barré syndrome [128]. Due to the few publications of cases in transplant patients, there is still no exact knowledge of the clinical picture, disease progression, and duration of viremia in this population. However, there are reports of an association with kidney graft dysfunction, but with complete recovery of function after resolution of the infection [127]. Diagnosis can be made through serology, but there are reports of cross-reaction with the dengue virus, which may result in false-positive tests for dengue. Treatment is limited to supportive measures.

35.8.5 Strongyloidiasis

Strongyloides stercoralis infection is endemic in Brazil, with estimated incidence of over 20% of the general population, and is therefore one of the most relevant helminthic diseases in the country [38, 129, 130]. In kidney transplantation, as in any solid organ transplantation, strongyloidiasis can have a catastrophic evolution, which justifies the discussion of prophylactic strategies and a better understanding of this infection in this specific population. The disease can occur through the reactivation of a preexisting chronic intestinal infection, which is the most frequent form in transplant recipients, followed by de novo acquisition in endemic areas and, eventually, transmission through the graft [38, 62, 131, 132].

Clinically, four forms of infection can be identified [129, 133–136]: acute, chronic intestinal, hyperinfection syndrome, and disseminated strongyloidiasis. The acute form is characterized by nonspecific abdominal pain, generally associated with nausea, vomiting, and, more frequently, diarrhea. Skin lesions and signs of lung involvement, such as dry cough and wheezing, which characterize *Loeffler 's syndrome,* may occur sporadically. The chronic intestinal form, which is more frequent, is characterized by nonspecific and intermittent signs and symptoms such as anorexia, diarrhea, constipation, abdominal pain, and epigastric pain. In more severe but rare cases, it may progress to malabsorption syndrome, paralytic ileus, intestinal obstruction, duodenal obstruction, and gastrointestinal bleeding. The accentuation of the intestinal condition, associated with more severe pulmonary manifestations, such as dyspnea and hemoptysis, occurs in hyperinfection syndrome, when there is an amplification in the normal life cycle of *Strongyloides stercoralis*, accompanied by a large number of larvae in the duodenum, which migrate to the lungs via the venous system. In these three forms, the helminth larvae are found only in sites of their usual life cycle. Finally, in disseminated strongyloidiasis, the clinical picture of hyperinfection syndrome is associated with other systemic complications, such as meningitis, cholecystitis, liver abscess, pancreatitis, or septic shock, and the larvae are found in sites outside their natural life cycle. Severe forms have mortality rates higher than 50% and are more frequent in individuals using immunosuppressants, especially in those with intensified immunosuppression, such as that which occurs at the beginning of transplantation, or after treatment of episodes of acute rejection [61, 133].

The clinical picture in transplant recipients is quite nonspecific, but in general there are symptoms of involvement of the gastrointestinal tract, which can be confused with other types of infections common in the first months after transplan-

tation, such as that caused by cytomegalovirus. However, abdominal distension and signs of acute abdomen are more frequently found, with progression to severe sepsis and septic shock. The degree of suspicion should be high and empirical treatment cannot be delayed. Diagnosis can be based on parasitological, serological, or histological methods, however, in this population it occurs more frequently by identification of the larva in body fluids, such as tracheal aspirate, bronchoalveolar lavage, pleural fluid, urine, cerebrospinal fluid, and peritoneal fluid [137].

Treatment of acute or chronic intestinal infection is preferably done with ivermectin for 2 days or, alternatively, with albendazole for 3 days, and the regimen should be repeated in 1 week [138, 139]. In hyperinfection or disseminated disease, the choice is ivermectin and the treatment time depends on the clinical evolution, on average extending for 10–14 days. In severe cases, when oral ingestion is not possible, the rectal route can be used, or even the parenteral formulation for veterinary use, subcutaneously, can be considered [136, 140]. As previously described, prophylaxis should be instituted for all kidney transplant recipients, preferably with ivermectin for 2 days, 2 weeks before transplantation in the case of living donor recipients, or immediately after surgery in any case, as well as after treatment of episodes of acute rejection, or the need for intensification of immunosuppression for any other reason.

References

1. Cusumano AM, Di Gioia C, Hermida O, Lavorato C, Latin American Registry of D, Renal T. The Latin American dialysis and renal transplantation registry annual report 2002. Kidney Int Suppl. 2005;97:S46–52.
2. de Castro Rodrigues Ferreira F, Cristelli MP, Paula MI, Proenca H, Felipe CR, Tedesco-Silva H, et al. Infectious complications as the leading cause of death after kidney transplantation: analysis of more than 10,000 transplants from a single center. J Nephrol. 2017;30(4):601–6.
3. El-Zoghby ZM, Stegall MD, Lager DJ, Kremers WK, Amer H, Gloor JM, et al. Identifying specific causes of kidney allograft loss. Am J Transplant. 2009;9(3):527–35.
4. ANZDATA 46th Annual Report 2023 (Date to 2022). 2023. https://www.anzdata.org.au/report/anzdata-46th-annual-report-2023-data-to-2022/.
5. Death with a functioning graft – CTS newsletters 2012. Available from: http://www.ctstransplant.org/public/newsletters/2012/png/2012-2.html?ts=9334835325429464.
6. Requiã o-Moura LR, Daher EF, Moreira Albino CR, de Oliveira Brilhante S, da Silva Junior GB, Costa SD, et al. Tropical infections in the context of kidney transplantation in Latin America. Am J Trop Med Hyg. 2021;105(3):564–72.
7. Medina-Pestana JO, Duro-Garcia V. Strategies for establishing organ transplant programs in developing countries: the Latin America and Caribbean experience. Artif Organs. 2006;30(7):498–500.
8. Machado CM, Martins TC, Colturato I, Leite MS, Simione AJ, Souza MP, et al. Epidemiology of neglected tropical diseases in transplant recipients. Review of the literature and experience of a Brazilian HSCT center. Rev Inst Med Trop Sao Paulo. 2009;51(6):309–24.
9. Franco-Paredes C, Jacob JT, Hidron A, Rodriguez-Morales AJ, Kuhar D, Caliendo AM. Transplantation and tropical infectious diseases. Int J Infect Dis. 2010;14(3):e189–96.
10. Kotton CN. Zoonoses in solid-organ and hematopoietic stem cell transplant recipients. Clin Infect Dis. 2007;44(6):857–66.
11. Barsoum RS. Parasitic infections in transplant recipients. Nat Clin Pract Nephrol. 2006;2(9):490–503.
12. Valar C, Keitel E, Dal Pra RL, Gnatta D, Santos AF, Bianco PD, et al. Parasitic infection in renal transplant recipients. Transplant Proc. 2007;39(2):460–2.
13. Machado CM, Levi JE. Transplant-associated and blood transfusion-associated tropical and parasitic infections. Infect Dis Clin N Am. 2012;26(2):225–41.
14. Motta IJ, Spencer BR, Cordeiro da Silva SG, Arruda MB, Dobbin JA, Gonzaga YB, et al. Evidence for transmission of Zika virus by platelet transfusion. N Engl J Med. 2016;375(11):1101–3.
15. Fishman JA. Infection in organ transplantation. Am J Transplant. 2017;17:856.
16. Martin-Davila P, Fortun J, Lopez-Velez R, Norman F, Montes de Oca M, Zamarron P, et al. Transmission of tropical and geographically restricted infections during solid-organ transplantation. Clin Microbiol Rev. 2008;21(1):60–96.
17. Sawyer RG, Crabtree TD, Gleason TG, Antevil JL, Pruett TL. Impact of solid organ transplantation and immunosuppression on fever, leukocytosis, and physiological response during bacterial and fungal infections. Clin Transpl. 1999;13(3):260–5.
18. Mahmoud KM, Sobh MA, El-Agroudy AE, Mostafa FE, Baz ME, Shokeir AA, et al. Impact of schistosomiasis on patient and graft outcome after renal transplantation: 10 years' follow-up. Nephrol Dial Transplant. 2001;16(11):2214–21.
19. Boulware DR, Stauffer WM, Hendel-Paterson BR, Rocha JL, Seet RC, Summer AP, et al. Maltreatment

of Strongyloides infection: case series and worldwide physicians-in-training survey. Am J Med. 2007;120(6):545. e1–8.
20. Duvignaud A, Receveur MC, Ezzedine K, Pistone T, Malvy D. Visceral leishmaniasis due to Leishmania infantum in a kidney transplant recipient living in France. Travel Med Infect Dis. 2015;13(1):115–6.
21. Nuesch R, Cynke E, Jost MC, Zimmerli W. Thrombocytopenia after kidney transplantation. Am J Kidney Dis. 2000;35(3):537–8.
22. Weerakkody RM, Patrick JA, Sheriff MH. Dengue fever in renal transplant patients: a systematic review of literature. BMC Nephrol. 2017;18(1):15.
23. Carrillo E, Carrasco-Anton N, Lopez-Medrano F, Salto E, Fernandez L, San Martin JV, et al. Cytokine release assays as tests for exposure to Leishmania, and for confirming cure from Leishmaniasis, in solid organ transplant recipients. PLoS Negl Trop Dis. 2015;9(10):e0004179.
24. Redelman-Sidi G, Sepkowitz KA. IFN-gamma release assays in the diagnosis of latent tuberculosis infection among immunocompromised adults. Am J Respir Crit Care Med. 2013;188(4):422–31.
25. Costa SD, de Sandes-Freitas TV, Jacinto CN, Martiniano LVM, Amaral YS, Paes F, et al. Tuberculosis after kidney transplantation is associated with significantly impaired allograft function. Transpl Infect Dis. 2017;19(5)
26. Viana LA, Cristelli MP, Santos DW, Tavares MG, Dantas MTC, Felipe CR, et al. Influence of epidemiology, immunosuppressive regimens, clinical presentation, and treatment on kidney transplant outcomes of patients diagnosed with tuberculosis: a retrospective cohort analysis. Am J Transplant. 2019;19(5):1421–31.
27. San-Juan R, De Dios B, Navarro D, García - Reyne A, Lumbreras C, Bravo D, et al. Epstein-Barr virus DNAemia is an early surrogate marker of the net state of immunosuppression in solid organ transplant recipients. Transplantation. 2013;95(5):688–93.
28. Clemente W, Vidal E, Girao E, Ramos AS, Govedic F, Merino E, et al. Risk factors, clinical characteristics and outcomes of visceral leishmaniasis in solid-organ transplant recipients: a retrospective multicenter case-control study. Clin Microbiol Infect. 2015;21(1):89–95.
29. Ross AG, Bartley PB, Sleigh AC, Olds GR, Li Y, Williams GM, et al. Schistosomiasis. N Engl J Med. 2002;346(16):1212–20.
30. Silva GBDJ, Pinto JR, Barros EJG, Farias GMN, Daher EF. Kidney involvement in malaria: an update. Rev Inst Med Trop Sao Paulo. 2017;59:e53.
31. Daher Ede F, Junior Silva GB, Vieira AP, Souza JB, Falcao Fdos S, Costa CR, et al. Acute kidney injury in a tropical country: a cohort study of 253 patients in an infectious diseases intensive care unit. Rev Soc Bras Med Trop. 2014;47(1):86–9.
32. Daher Ede F, de Abreu KL, da Silva Junior GB. Leptospirosis-associated acute kidney injury. J Bras Nefrol. 2010;32(4):400–7.
33. Jasenosky LD, Scriba TJ, Hanekom WA, Goldfeld AE. T cells and adaptive immunity to Mycobacterium tuberculosis in humans. Immunol Rev. 2015;264(1):74–87.
34. Chen CY, Liu CJ, Feng JY, Loong CC, Liu C, Hsia CY, et al. Incidence and risk factors for tuberculosis after liver transplantation in an endemic area: a nationwide population-based matched cohort study. Am J Transplant. 2015;15(8):2180–7.
35. Guirao-Arrabal E, Santos F, Redel-Montero J, Vaquero JM, Cantisan S, Vidal E, et al. Risk of tuberculosis after lung transplantation: the value of pretransplant chest computed tomography and the impact of mTOR inhibitors and azathioprine use. Transpl Infect Dis. 2016;18(4):512–9.
36. Vale S. Reactivation versus clearance of Mycobacterium tuberculosis using mammalian target of rapamycin inhibitors in patients with cancer can be context dependent. J Clin Oncol. 2013;31(20):2634.
37. Durrbach A, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant. 2010;10(3):547–57.
38. Keizer PB, Nutman TB. Strongyloides stercoralis in the immunocompromised population. Clin Microbiol Rev. 2004;17(1):208–17.
39. Matsuzawa K, Nakamura F, Abe M, Okamoto K. Immunosuppressive and antiparasitic effects of cyclosporin A on Hymenolepis nana infection in mice. Int J Parasitol. 1998;28(4):579–88.
40. Munro GH, Brannan LR, Chappell LH, Thomson AW, McLaren DJ. The larvicidal activity of cyclosporin A against Schistosoma mansoni in mice. Parasitology. 1991;102(Pt 1):57–63.
41. Schad GA. Cyclosporine may eliminate the threat of overwhelming strongyloidiasis in immunosuppressed patients. J Infect Dis. 1986;153(1):178.
42. Qing M, Yang F, Zhang B, Zou G, Robida JM, Yuan Z, et al. Cyclosporine inhibits flavivirus replication through blocking the interaction between host cyclophilins and viral NS5 protein. Antimicrob Agents Chemother. 2009;53(8):3226–35.
43. Munoz L, Santin M. Prevention and management of tuberculosis in transplant recipients: from guidelines to clinical practice. Transplantation. 2016;100(9):1840–52.
44. Santoro-Lopes G, Subramanian AK, Molina I, Aguado JM, Rabagliatti R, Len O. Tuberculosis recommendations for solid organ transplant recipients and donors. Transplantation. 2018;102(2S Suppl 2):S60–S5.
45. Jha V, Chugh KS. Posttransplant infections in tropical countries. Artif Organs. 2002;26(9):770–7.
46. van Griensven J, Carrillo E, Lopez-Velez R, Lynen L, Moreno J. Leishmaniasis in immunosuppressed individuals. Clin Microbiol Infect. 2014;20(4):286–99.
47. Brazil. Ministry of Health. Secretariat of Health Care. Department of Specialized and Thematic

Care. Clinical Guidelines for the Care of Patients with Chronic Kidney Disease – CKD in the Unified Health System/Ministry of Health. Secretariat of Health Care. Department of Specialized and Thematic Care. – Brasília: Ministry of Health, 2014. p.: 37 p.: ill.
48. (ABTO) CdieTCdABdTd Ó. Vaccination before and after organ transplantation in adults. https://site.abto.org.br/wp-content/uploads/2024/02/ABTO2024_recomendacoes-vacinacao_18dez23.pdf2024.
49. ACoIPA. Recommended Vaccinations for Adults, Easy-To-Read Format https://www.cdc.gov/vaccines/schedules/easy-to-read/adult-easyread.html2024.
50. Ordinance No. 2,600 – technical regulation of the National Transplant System; 2009.
51. Fischer SA, Avery RK, Practice AIDCo. Screening of donor and recipient prior to solid organ transplantation. Am J Transplant. 2009;9(Suppl 4):S7–18.
52. Mello MA, da Conceição AF, Sousa SM, Alc ântara LC, Marin LJ, Regina da Silva Raiol M, et al. HTLV-1 in pregnant women from Southern Bahia, Brazil: a neglected condition despite the high prevalence. Virol J. 2014;11:28.
53. Morais MPE, Gato CM, Maciel LA, Lalwani P, Costa CA, Lalwani JDB. Prevalence of human T-lymphotropic virus type 1 and 2 among blood donors in Manaus, Amazonas State, Brazil. Rev Inst Med Trop Sao Paulo. 2017;59:e80.
54. Tedla F, Brar A, John D, Sumrani N. Risk of transmission of human T-lymphotropic virus through transplantation. Am J Transplant. 2015;15(4):1123–4.
55. Dosik H, Goldstein MF, Poiesz BJ, Williams L, Fahnrich B, Ehrlich GD, et al. Seroprevalence of human T-lymphotropic virus in blacks from a selected central Brooklyn population. Cancer Investig. 1994;12(3):289–95.
56. Moreno-Ajona D, Yuste JR, Martín P, Gállego Pérez - Larraya J. HTLV-1 myelopathy after renal transplant and antiviral prophylaxis: the need for screening. J Neurovirol. 2018;24(4):523–5.
57. CDMEADTES, CMATS/CGGTS/DGITIS/SCTIE/MS. Recommendation Report No. 573 – Interferon -gamma release test (interferon gamma release assay (IGRA) for detection of tuberculosis latent in immunocompromised patients. https://www.gov.br/conitec/pt-br/midias/consultas/relatorios/2020/20201113_relatorio_de_recomendacao_573_igra.pdf2020.
58. Pierrotti LC, Kotton CN. Transplantation in the tropics: lessons on prevention and management of tropical infectious diseases. Curr Infect Dis Rep. 2015;17(7):492.
59. Clemente WT, Pierrotti LC, Abdala E, Morris MI, Azevedo LS, Lopez-Velez R, et al. Recommendations for management of endemic diseases and travel medicine in solid-organ transplant recipients and donors: Latin America. Transplantation. 2018;102(2):193–208.
60. Subramanian A, Dorman S, Practice AIDCo. Mycobacterium tuberculosis in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S57–62.
61. Kotton CN, Lattes R. Parasitic infections in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S234–51.
62. Camargo LFA, Kamar N, Gotuzzo E, Wright AJ. Schistosomiasis and Strongyloidiasis recommendations for solid-organ transplant recipients and donors. Transplantation. 2018;102(2S Suppl 2):S27–34.
63. de Castro Lima Santos DW, Stucchi RSB, Trindade Clemente W, Abdala E, Santoro-Lopes G, Pierrotti L. Recommendations for donor and recipient dengue screening in solid organ transplantation. Braz J Transplant. 2024:27.
64. Clemente WT, Mourao PHO, Lopez-Medrano F, Schwartz BS, Garcia-Donoso C, Torre-Cisneros J. Visceral and cutaneous Leishmaniasis recommendations for solid organ transplant recipients and donors. Transplantation. 2018;102(2S Suppl 2):S8–S15.
65. Copeland NK, Aronson NE. Leishmaniasis: treatment updates and clinical practice guidelines review. Curr Opin Infect Dis. 2015;28(5):426–37.
66. Pierrotti LC, Levi ME, Di Santi SM, Segurado AC, Petersen E. Malaria disease recommendations for solid organ transplant recipients and donors. Transplantation. 2018;102(2S Suppl 2):S16–26.
67. Meinerz G, da Silva CK, Goldani JC, Garcia VD, Keitel E. Epidemiology of tuberculosis after kidney transplantation in a developing country. Transpl Infect Dis. 2016;18(2):176–82.
68. Marques ID, Azevedo LS, Pierrotti LC, Caires RA, Sato VA, Carmo LP, et al. Clinical characteristics and outcomes of tuberculosis in kidney transplant recipients in Brazil: a report of the last decade. Clin Transpl. 2013;27(2):E169–76.
69. Antinori S, Cascio A, Parravicini C, Bianchi R, Corbellino M. Leishmaniasis among organ transplant recipients. Lancet Infect Dis. 2008;8(3):191–9.
70. Oliveira CM, Oliveira ML, Andrade SC, Girao ES, Ponte CN, Mota MU, et al. Visceral leishmaniasis in renal transplant recipients: clinical aspects, diagnosis problems, and response to treatment. Transplant Proc. 2008;40(3):755–60.
71. Alves da Silva A, Pacheco-Silva A, de Castro Cintra Sesso R, Esmeraldo RM, Costa de Oliveira CM, Fernandes PF, et al. The risk factors for and effects of visceral leishmaniasis in graft and renal transplant recipients. Transplantation 2013;95(5):721–727.
72. de Silva AA, Pacheco e Silva Filho A, Sesso Rde C, Esmeraldo Rde M, de Oliveira CM, Fernandes PF, et al. Epidemiologic, clinical, diagnostic and therapeutic aspects of visceral leishmaniasis in renal transplant recipients: experience from thirty cases. BMC Infect Dis. 2015;15:96.

73. Bern C. Chagas' disease. N Engl J Med. 2015;373(5):456–66.
74. ReC S-L, Barbosa M, Coura JR, Arcanjo AR, AaS N, Ferreira JM, et al. Outbreak of acute Chagas disease associated with oral transmission in the Rio Negro region, Brazilian Amazon. Rev Soc Bras Med Trop. 2013;46(4):510–4.
75. Prata A. Clinical and epidemiological aspects of Chagas disease. Lancet Infect Dis. 2001;1(2):92–100.
76. Huprikar S, Bosserman E, Patel G, Moore A, Pinney S, Anyanwu A, et al. Donor-derived Trypanosoma cruzi infection in solid organ recipients in the United States, 2001-2011. Am J Transplant. 2013;13(9):2418–25.
77. Riarte A, Luna C, Sabatiello R, Sinagra A, Schiavelli R, De Rissio A, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989–1996. Clin Infect Dis. 1999;29(3):561–7.
78. Schmunis GA, Yadon ZE. Chagas disease: a Latin American health problem becoming a world health problem. Acta Trop. 2010;115(1–2):14–21.
79. Cicora F, Escurra V, Silguero S, González IM, Roberti JE. Use of kidneys from trypanosoma cruzi-infected donors in naive transplant recipients without prophylactic therapy: the experience in a high-risk area. Transplantation. 2014;97(1):e3–4.
80. Sousa AA, Lobo MC, Barbosa RA, Bello V. Chagas seropositive donors in kidney transplantation. Transplant Proc. 2004;36(4):868–9.
81. Wendel S. Transfusion transmitted Chagas disease: is it really under control? Acta Trop. 2010;115(1–2):28–34.
82. Lattes R, Lasala MB. Chagas disease in the immunosuppressed patient. Clin Microbiol Infect. 2014;20(4):300–9.
83. Pierrotti LC, Carvalho NB, Amorin JP, Pascual J, Kotton CN, López-Vélez R. Chagas disease recommendations for solid-organ transplant recipients and donors. Transplantation. 2018;102(2S Suppl 2):S1–7.
84. Kransdorf EP, Zakowski PC, Kobashigawa JA. Chagas disease in solid organ and heart transplantation. Curr Opin Infect Dis. 2014;27(5):418–24.
85. Campos SV, Strabelli TM, Amato Neto V, Silva CP, Bacal F, Bocchi EA, et al. Risk factors for Chagas' disease reactivation after heart transplantation. J Heart Lung Transplant. 2008;27(6):597–602.
86. Pinazo MJ, Miranda B, Rodríguez-Villar C, Altclas J, Brunet Serra M, Garc í a-Otero EC, et al. Recommendations for management of Chagas disease in organ and hematopoietic tissue transplantation programs in nonendemic areas. Transplant Rev (Orlando). 2011;25(3):91–101.
87. Bacal F, Silva CP, Bocchi EA, Pires PV, Moreira LF, Issa VS, et al. Mychophenolate mofetil increased chagas disease reactivation in heart transplant patients: comparison between two different protocols. Am J Transplant. 2005;5(8):2017–21.
88. Bestetti RB, Souza TR, Lima MF, Theodoropoulos TA, Cordeiro JA, Burdmann EA. Effects of a mycophenolate mofetil-based immunosuppressive regimen in Chagas' heart transplant recipients. Transplantation. 2007;84(3):441–2.
89. Barquilla A, Crespo JL, Navarro M. Rapamycin inhibits trypanosome cell growth by preventing TOR complex 2 formation. Proc Natl Acad Sci USA. 2008;105(38):14579–84.
90. Ortiz AM, Troncoso P, Sainz M, Vilches S. Prophylaxis and treatment of Chagas disease in renal transplant donor and recipient: case report. Transplant Proc. 2010;42(1):393–4.
91. Cáceres Munar BA, Urbina A, Ortíz T, Rodríguez A, Fernández OL, Ospina LF, et al. High prevalence of dengue, Zika, and chikungunya viruses in blood donors during a dengue outbreak and an endemic period in Colombia. Front Med (Lausanne). 2024;11:1380129.
92. World Health Organization. Dengue guidelines for diagnosis, treatment, prevention and control. new ed. Geneva: World Health Organization; 2009.
93. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504–7.
94. Nasim A, Anis S, Baqi S, Akhtar SF, Baig-Ansari N. Clinical presentation and outcome of dengue viral infection in live-related renal transplant recipients in Karachi, Pakistan. Transpl Infect Dis. 2013;15(5):516–25.
95. Costa SD, da Silva GB, Jacinto CN, Martiniano LV, Amaral YS, Paes FJ, et al. Dengue fever among renal transplant recipients: a series of 10 cases in a tropical country. Am J Trop Med Hyg. 2015;93(2):394–6.
96. Fernandes PF, Siqueira RA, Girão ES, Mota MU, Marques LC, Andrade SC, et al. Dengue in renal transplant recipients: clinical course and impact on renal function. World J Transplant. 2017;7(1):57–63.
97. Guzman MG, Gubler DJ, Izquierdo A, Martinez E, Halstead SB. Dengue infection. Nat Rev Dis Primers. 2016;2:16055.
98. Guzman MG, Harris E. Dengue. Lancet. 2015;385(9966):453–65.
99. Narvaez F, Gutierrez G, Pérez MA, Elizondo D, Nuñez A, Balmaseda A, et al. Evaluation of the traditional and revised WHO classifications of dengue disease severity. PLoS Negl Trop Dis. 2011;5(11):e1397.
100. Lovera D, Araya S, Mesquita MJ, Avalos C, Ledesma S, Arbo A. Prospective applicability study of the new dengue classification system for clinical management in children. Pediatr Infect Dis J. 2014;33(9):933–5.
101. Maia SH, Brasil IR, ReM E, Ponte CN, Costa RC, Lira RA. Severe dengue in the early postoperative period after kidney transplantation: two case reports from hospital Geral de Fortaleza. Rev Soc Bras Med Trop. 2015;48(6):783–5.
102. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, et al. Dengue: a continuing global threat. Nat Rev Microbiol. 2010;8(12 Suppl):S7–16.

103. Tang KF, Ooi EE. Diagnosis of dengue: an update. Expert Rev Anti-Infect Ther. 2012;10(8):895–907.
104. Shaji Mathew J, Menon VP, Mallick S, Sivasankara Pillai Thankamony Amma B, Balakrishnan D, Gopalakrishnan U, et al. Dengue virus transmission from live donor liver graft. Am J Transplant. 2019;19(6):1838–46.
105. Saigal S, Choudhary NS, Saraf N, Kataria S, Mohanka R, Soin AS. Transmission of dengue virus from a donor to a recipient after living donor liver transplantation. Liver Transpl. 2013;19(12):1413–4.
106. Rosso F, Pineda JC, Sanz AM, Cedano JA, Caicedo LA. Transmission of dengue virus from deceased donors to solid organ transplant recipients: case report and literature review. Braz J Infect Dis. 2018;22(1):63–9.
107. Lecadieu A, Teysseyre L, Larsen K, Vidal C, Caron M, Traversier N, et al. Case report: transmission of dengue virus from a deceased donor to a kidney transplant recipient previously infected by dengue virus. Am J Trop Med Hyg. 2021;104(6):2199–201.
108. Robinson MC. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952–53. I. Clinical features. Trans R Soc Trop Med Hyg. 1955;49(1):28–32.
109. Rodrigues Faria N, Lourenço J, Marques de Cerqueira E, Maia de Lima M, Pybus O, Carlos Junior Alcantara L. Epidemiology of chikungunya virus in Bahia, Brazil, 2014–2015. PLoS Curr. 2016;8.
110. de Souza WM, Ribeiro GS, de Lima STS, de Jesus R, Moreira FRR, Whittaker C, et al. Chikungunya: a decade of burden in the Americas. Lancet Reg Health Am. 2024;30:100673.
111. Darrigo LG Jr, de Sant'Anna Carvalho AM, Machado CM. Chikungunya, dengue, and Zika in immunocompromised hosts. Curr Infect Dis Rep. 2018;20(4):5.
112. Pierrotti LC, Lopes M, Nascimento APD, Caiaffa-Filho H, Lemos FBC, Reusing JO Jr, et al. Chikungunya in kidney transplant recipients: a series of cases. Int J Infect Dis. 2017;64:96–9.
113. Girão ES, Rodrigues Dos Santos BG, do Amaral ES, Costa PEG, Pereira KB, de Araujo Filho AH, et al. Chikungunya infection in solid organ transplant recipients. Transplant Proc. 2017;49(9):2076–81.
114. Moro ML, Grilli E, Corvetta A, Silvi G, Angelini R, Mascella F, et al. Long-term chikungunya infection clinical manifestations after an outbreak in Italy: a prognostic cohort study. J Infect. 2012;65(2):165–72.
115. McCarthy MK, Morrison TE. Chronic chikungunya virus musculoskeletal disease: what are the underlying mechanisms? Future Microbiol. 2016;11(3):331–4.
116. Staikowsky F, Talarmin F, Grivard P, Souab A, Schuffenecker I, Le Roux K, et al. Prospective study of Chikungunya virus acute infection in the Island of La Réunion during the 2005–2006 outbreak. PLoS One. 2009;4(10):e7603.
117. Kee AC, Yang S, Tambyah P. Atypical chikungunya virus infections in immunocompromised patients. Emerg Infect Dis. 2010;16(6):1038–40.
118. Dave R, Patel M, Kumar D, Patil M, Tambi P, Parmar V, et al. A comparative analysis of chikungunya in kidney transplant recipients compared with the general population: a multicenter, retrospective, cohort study from India. Exp Clin Transplant. 2023;21(9):722–6.
119. Tavares BM, Fernandes PF, Oliveira CMC, Silva SL, Mota MU, Andrade TH, et al. Chikungunya on kidney transplant recipients: is it the same? Transplantation. 2019;103(2):441–5.
120. Machado CM, Pereira BBS, Felix AC, Oliveira MC, Darrigo LG Jr, de Souza MP, et al. Zika and chikungunya virus infections in hematopoietic stem cell transplant recipients and oncohematological patients. Blood Adv. 2017;1(10):624–7.
121. Cunha RVD, Thirty KS. Chikungunya virus: clinical aspects and treatment – a review. Mem Inst Oswaldo Cruz. 2017;112(8):523–31.
122. Delang L, Segura Guerrero N, Tas A, Quérat G, Pastorino B, Froeyen M, et al. Mutations in the chikungunya virus non-structural proteins cause resistance to favipiravir (T-705), a broad-spectrum antiviral. J Antimicrob Chemother. 2014;69(10):2770–84.
123. Briolant S, Garin D, Scaramozzino N, Jouan A, Crance JM. In vitro inhibition of Chikungunya and Semliki Forest viruses replication by antiviral compounds: synergistic effect of interferon-alpha and ribavirin combination. Antivir Res. 2004;61(2):111–7.
124. Zika virus outbreaks in the Americas. Wkly Epidemiol Rec. 2015;90(45):609–10.
125. Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. Emerg Infect Dis. 2015;21(1):84–6.
126. Jimenez A, Shaz BH, Kessler D, Bloch EM. How do we manage blood donors and recipients after a positive Zika screening result? Transfusion. 2017;57(9):2077–83.
127. Nogueira ML, Estofolete CF, Terzian AC, Mascarin do Vale EP, da Silva RC, da Silva RF, et al. Zika virus infection and solid organ transplantation: a new challenge. Am J Transplant. 2017;17(3):791–5.
128. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika virus associated with microcephaly. N Engl J Med. 2016;374(10):951–8.
129. Abdalhamid BA, Al Abadi AN, Al Saghier MI, Joudeh AA, Shorman MA, Amr SS. Strongyloides stercoralis infection in kidney transplant recipients. Saudi J Kidney Dis Transpl. 2015;26(1):98–102.
130. Marcos LA, Terashima A, Canales M, Gotuzzo E. Update on strongyloidiasis in the immunocompromised host. Curr Infect Dis Rep. 2011;13(1):35–46.
131. Abanyie FA, Gray EB, Delli Carpini KW, Yanofsky A, McAuliffe I, Rana M, et al. Donor-derived Strongyloides stercoralis infection in solid organ transplant recipients in the United States, 2009–2013. Am J Transplant. 2015;15(5):1369–75.

132. Rego Silva J, Macau RA, Mateus A, Cruz P, Aleixo MJ, Brito M, et al. Successful treatment of Strongyloides stercoralis Hyperinfection in a kidney transplant recipient: case report. Transplant Proc. 2018;50(3):861–6.
133. Ferreira CJ, Silva DA, Almeida PH, Silva LS, Carvalho VP, Coutinho AF, et al. Fatal disseminated strongyloidiasis after kidney transplantation. Rev Soc Bras Med Trop. 2012;45(5):652–4.
134. Buonfrate D, Requena-Mendez A, Angheben A, Muñoz J, Gobbi F, Van Den Ende J, et al. Severe strongyloidiasis: a systematic review of case reports. BMC Infect Dis. 2013;13:78.
135. Khuroo MS. Hyperinfection strongyloidiasis in renal transplant recipients. BMJ Case Rep. 2014;2014:bcr2014205068.
136. Donadello K, Cristallini S, Taccone FS, Lorent S, Vincent JL, de Backer D, et al. Strongyloides disseminated infection successfully treated with parenteral ivermectin: case report with drug concentration measurements and review of the literature. Int J Antimicrob Agents. 2013;42(6):580–3.
137. Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis infection. Clin Infect Dis. 2001;33(7):1040–7.
138. Suputtamongkol Y, Premasathian N, Bhumimuang K, Waywa D, Nilganuwong S, Karuphong E, et al. Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloidiasis. PLoS Negl Trop Dis. 2011;5(5):e1044.
139. Marti H, Haji HJ, Savioli L, Chwaya HM, Mgeni AF, Ameir JS, et al. A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of Strongyloides stercoralis and other soil-transmitted helminth infections in children. Am J Trop Med Hyg. 1996;55(5):477–81.
140. Suputtamongkol Y, Kungpanichkul N, Silpasakorn S, Beeching NJ. Efficacy and safety of a single-dose veterinary preparation of ivermectin versus 7-day high-dose albendazole for chronic strongyloidiasis. Int J Antimicrob Agents. 2008;31(1):46–9.

Index

A
AbTX1 toxin, 132
Acetaminophen, 65
Acid-fast bacilli (AFB), 332
Acquired immunodeficiency syndrome (AIDS), 332
Acute diffuse glomerulonephritis (ADG), 291
Acute interstitial nephritis (AIN), 189
Acute kidney injury (AKI), 258, 341
  causes of, 185
  and Chagas disease, 219
  and chikungunya, 150
  classification, 29–32
  definition, 185, 303
  differential diagnosis of, 326
  and dehydration, 29
  due to ant bites, 128
  due to scorpion sting, 114–116
  and heat stress, 31–32
  and herbal medicine, 79
  in HIV patients, 185
  with leprosy glomerulonephritis, 310
  in malaria, 280
  in patients with schistosomiasis, 233
  in patients with visceral leishmaniasis, 273
  in people living with HIV, 183
  in PLWH, 185
  recognition strategies in tropics, 11–14
  in tetanus infection, 326
  leptospirosis, 320
  multifactorial etiology, 326
  pathophysiology of, 327
Acute opioid poisoning, 70
Acute reference dose (ARfD), 87
Acute tubular necrosis, 284
Acyclovir, 190
ADAMTS 13, 282
Aedes aegypti, 152, 155, 161
Age, 10
Agrochemicals, 44, 364
AIDS-related illnesses, 183
Air pollution, 21, 42, 44, 46
Albumin-creatinine ratio, 47
Albuminuria, 342
Alcohol consumption, 71
Allergen, ant venom, 127
Alphavirus genus, 148
American cutaneous leishmaniasis (ACL)
  diagnosis, 259
  kidney impairment in, 258
  local therapy, 263
  miltefosine, 263
  oral systemic therapy, 263
  pentavalent antimonial, 262–263
  pentoxifylline, 263
  pre-and post-desmopressin U_{osm} in patients with, 260
  treatment, 262
  tubular defects, 259
American cutaneous leishmaniasis (ACL) periurban type, 254
American trypanosomiasis, *see* Chagas disease
Amphotericin B, 185, 263
Amphotericin B deoxycholate, 263
Amphotericin B-associated acute kidney injury, 271
Anaphylaxis
  ant venom, 127
  marine toxins, 135
Anemia, 269
Anemones, 132, 134
Angiotensin-converting enzyme (ACE) inhibitors, 187, 201
Angiotensin-receptor blockers (ARBs), 187
Animal toxin poisoning, 113
Ant venom
  applications, 129
  composition, 127
  nephrotoxicity, 128
Anthosoas, 132
Antibiotics, in leptospirosis, 320
Anti-cathepsin G, 282
Antiepileptic drugs, 65
Antigen-presenting cells (APCs), 273
Antimalarial treatment, 281, 283–284
Anti-neutrophil cytoplasmic antibodies (ANCA), 282
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, 305
Antipsychotic drug-induced nephropathy, 67

© The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Switzerland AG 2025
G. Bezerra da Silva Junior et al. (eds.), *Tropical Nephrology*, Sustainable Development Goals Series, https://doi.org/10.1007/978-3-031-94777-3

Antiretroviral drug renal toxicity, 189
Antiretroviral therapy (ART), 183, 185, 186
Antivenom (AV) treatment, 101
of crotalic envenomations, 105
APOL1-related CKD, 363, 367
Apolipoprotein L1 gene (*APOL1*), 186
Aquaporin (AQP2), 261
Arboviruses, 376
characteristics, 147
and kidney transplant recipients, 380–383
Arginine vasopressin (AVP), 351
Aristolochic acids (AA), 54, 81
Arsenic, 47, 50
chronic toxicity, 51
nephrotoxicity, 50
poisoning, 50
water contamination, 50
Atazanavir, 190

B
Badejo, 86
β2-microglobulin (β2-MG), 47
Biomarkers, 12, 47, 66
of fibrosis, 45
of renal injury, 50
Biotoxins, 89
Bisphenol, 55
Bisphenol A, 55
Bladder dysfunction, 336
Blood urea nitrogen (BUN) levels, 366
Borbotoxins, 88
Bothrops envenomations
antivenom treatment of, 100–101
kidney injury in, 102
mechanism of action, 101
mechanisms of injury, 102–103
Bothrops poisoning and kidney injury, 99–103
Bowman's capsule, 281
Brugia malayi, 239
Brugia timori, 239
BTK2, 114
Bull's eye fish, 86

C
Cadmium, 47, 49, 50
Cape aloe, 80
Caterpillar poisoning, *see* Lonomism
CD4 cell count, 183
Cell adhesion molecules (CAMs), 45
Centruroides, 113
Chagas disease, 372
and benznidazole, 221
causes, 217
clinical manifestations, 218
complications, 217
diagnosis, 219
epidemiology, 217–218
kidney involvement
acute phase, 219–220
chronic phase, 220
and kidney transplant recipients, 378–380
and nifurtimox, 222
pathophysiology, 218, 221
transmission, 217
treatment, 221
Chagoma, 378
Charybdotoxin, 114
Chemical intoxication, 9
Chemical substances, 68
Chemical toxins, 9
Chikungunya, 147
and acute kidney injury, 150
causes, 148
clinical presentations, 149
epidemiology, 148
and kidney transplant recipients, 380–383
laboratory findings, 149
pathophysiology of renal involvement, 149
renal histopathological findings, 150–152
treatment, 152
worldwide distribution of, 148
Chinese herbs, 54
Chloroquine, 283, 286
Chromium, 53
Chronic kidney disease (CKD), 336, 359
and cardiovascular diseases, 43
classification of, 352
definition, 43
and dehydration, 29
environmental toxicity, 44
epidemiology of, 359–363
exogenous poisoning, 65
and genetics, 44
HCV, 206
and heavy metals, 47
and herbal medicine, 80–82
incidence, 32
incidence rate, 359
leprosy, 309
mortality, 32
non-traditional causes, 32
in patients with schistosomiasis, 232
in people living with HIV, 183
prevalence, 43
renal tuberculosis, 335
risk factors, 43
in snakebite envenomation, 107–108
in tropical countries, 359–363
of unknown etiology, in Brazil, 32
of unknown origin (CKDu), 359
agrochemicals, 364
APOL1-related CKD, 363
Central America, 360
clinical manifestations, 365–366
complications, 361
diagnosis, 365–366
Egypt, 362
El Salvador, 360

environmental and toxic causes, 363–364
environmental toxins, 364
genetic disease, 363
Guatemala, 361
hantavirus, 365
heat stress, 363
heavy metals in drinking water, 364
hotspots, 360
India, 362
infectious diseases, 364–365
KCNA10, 363
leptospirosis, 364
in LIC, 365
in LMIC, 365
Mexico, 362
in Nicaragua, 361
prevalence, 360
prognosis, 366–367
SLC13A3, 363
South Asia, 361
Sri Lanka, 361
subclinical rhabdomyolysis, 364
sub-Saharan Africa, 362
treatment, 361, 366–367
in tropical and non-tropical countries, 363
Chronic kidney disease epidemiology (CKD-EPI), 353
Chronic kidney injury (CKD), from cadmium, 49
Chronic tubulointerstitial nephritis, 45
Chyluria, 242, 244
Cicutoxin, 88
Circulating anodic antigen (CAA), 230
Circulating cathodic antigen (CCA), 230
Climate change, 19, 20
and acute kidney injury, 23
and cancer, 23
chronic kidney disease, 23
and DM, 23
effects of, 22
evidence of, 20
on cardiovascular disease, 24
on human health, 20–21
and kidney stones, 23
on kidney stone formation, 35
on tropical diseases, 24
WHO definition, 21
Climate-sensitive diseases (CSDs), 21
Clostridium tetani, 323
Cnidaria, kidney injury by, 134
Cniradian toxin, 132
Cockroft & Gault formula, 353
Collecting duct, 355
Community associated (CA-MRSA), 302
Comorbid conditions, 10
Coronavirus disease 2019 (COVID-19), 66, 296
Corticosteroids, with anti-TB treatment, 337
Crack cocaine, 70
Creatinine, 45, 184, 352, 354
Creatinine-based CKD-EPI, 354
Crescentic glomerulonephritis, 282
Crotalus poisoning and kidney injury, 103–106
Crush syndrome, 6
Cryoglobulinemic membranoproliferative glomerulonephritis, 205
Crystalluria, 190
Cubosoas, 132
Cutaneous leishmaniasis
antigens, 258
diagnosis of, 256
diffuse form, 258
localized, 257
localized cutaneous form, 257
mucosal form, 257–258
prevalence, 257
transmission, 254
Cystatin C, 354

D

D-dimer, 122
Dendritic cells, 255
Dengue, 8, 147, 372
causes, 152
clinical and laboratory manifestations, 152–153
epidemiology, 152
and kidney transplant recipients, 380–383
laboratory finding, 152
pathophysiology of renal involvement, 154
renal manifestations in, 153
treatment, 155
Dengue hemorrhagic fever (DHF), 154
Dermonecrosis, 121
Diabetic kidney disease, 42
Diethylcarbamazine (DEC), 246
Dioxins, 55
Distal twisted tubule, 355
Domoic acid, 132
Drug poisoning, 66
Drug-induced nephrotoxicity, 67
Drugs of abuse, 70–71

E

Earthquakes, 6
eGFR analysis, 184
Electrolyte alteration, 283
Electronic health systems, 12
Elephantiasis, 239, 242
Encephalopathy, 337
Endocrine disruptors, 55
Endogenous creatinine clearance (ECC), 352
Envenomation, 97, 139, 140, 142
Environmental factors, 5–6
Environmental pollution, 41, 46
and kidney damage, 42–45
and nephrotoxicity, 46
and risk factors for kidney disease, 42
Environmental toxins, 364
Ethambutol, 337
Ethylene glycol, 69
Exanthematous rashes, 147

Exogenous poisoning, 71
characteristics, 65
medicines, 66–67
Exposure factors, 8–10
Extrapulmonary tuberculosis, 332

F
Fanconi syndrome, 190
Favipiravir, 174
Filarial fever, 242
Fire ants, 127
Fish venoms, *see* Haff disease
Flaviviridae, 195
Flavonoids, 80
Fluid and electrolyte disorders, 9
Focal and segmental glomerulosclerosis (FSGS), 186
characteristics, 187
HIVAN, 186
idiopathic, 186
Focal glomerulosclerosis, 231
Focal segmental glomerulosclerosis, 204
Formic acid, in ants, 127
Fractional excretion of sodium, 355
Fungustoxin, 114

G
Genetic susceptibility, 10
Genotypes, 197
Global Programme for the Elimination of Lymphatic Filariasis (GPELF), 243
Glomerular damage, schistosomiasis, 230
Glomerular edema, 122
Glomerular filtration, 351, 352
Glomerular filtration rate, 43, 184, 201, 352
mathematical equations, 352
methods, 352
Glomerulonephritis, 54
and Chagas disease, 219
in leprosy, 308
membranoproliferative, 220
mesangial proliferative, 220
occurrence, 219
Glomerulopathies, 204
in malária, 281–283
renal tuberculosis and, 335
Glucose-6-phosphate dehydrogenase (G6PD) deficiency, 283
Glyphosate, 47, 65
Glyphosate poisoning, 54
Good-Pasture syndrome, 54
Graft-transmitted tuberculosis, 378
Granulomatosis with polyangiitis (GPA), 305

H
H1N1 virus infection, *see* Influenza A
Haff disease, 85
clinical and laboratory aspects, 90
clinical management, 91–92
environmental aspects, 89–90
epidemiology, 85–87
etiological hypotheses, 87–88
history of, 85–87
kidney dysfunction, 91
temporal distribution, 89
Hantavirus, 365
Hantavirus infections, *see* Orthohantavirus infection
Heat stress, 6
Heavy metal(s), 44, 69
nephrotoxicity, 46–47
poisoning, 69
Hematochyluria, 244
Hemiscorpius lepturus, 115
Hemodialysis, 285
and *Staphylococcus*, 302–303
Hemolysis, and spider venom, 121
Hemolytic uremic syndrome, 115, 116, 127, 211
Hemophagocytic syndrome (HFS), 281
Hemorrhagic fever with renal syndrome (HFRS), 165
Hepadnaviridae, 195
Hepatitis A virus (HAV)
clinical manifestations, 196
epidemiology, 195–196
kidney involvement in, 196
natural history, 196
socioeconomic status, 196
treatment, 196
Hepatitis B virus (HBV)
clinical manifestations, 198
epidemiology, 197
HBsAg-positive carriers, 200
kidney involvement, 198–200
in kidney transplant recipients, 200
natural history, 197–198
nucleoside analogues, 200
prevalence, 197
transmission, 197
treatment, 200–201
Hepatitis C virus (HCV), 197
clinical manifestations, 203–204
epidemiology, 202–203
genotypes, 202
histopathological findings, 206
and HIV coinfection, 206
kidney involvement, 204–206
natural history, 203
pathophysiology, 206
transplant patients, 207
treatment, 207
Hepatitis D virus (HDV)
clinical manifestations, 202
epidemiology, 201
incubation period, 201
kidney involvement, 202
treatment, 202
Hepatitis E virus (HEV), 195

characteristics, 208
clinical manifestations, 208
epidemiology, 207
genotypes, 207
kidney involvement, 208
treatment, 208–209
Herbal medicine
and acute kidney injury, 79
kidney damage from, 77–78
and kidney diseases treatment, 78
treatment of kidney diseases, 78–79
Herbal products, 54
Herpesviridae, 195
Hidrosoas, 132
HIV-associated chronic kidney disease, 187–188
HIV-associated drug nephrotoxicity, 188–189
HIV-associated kidney diseases, 184
HIV-associated nephropathy (HIVAN), 184, 186–187
HIV patients co-infected with syphilis, 343
Holotrichous-isorhiza nematocysts, 132
Hospital associated (HA-MRSA), 302
Human immunodeficiency virus (HIV), 183, 197, 332
Human malaria, 279
Hydrocele, 242
Hydroelectrolytic balance, 29
Hyperglobulinemia, 269
Hyperkalemia, 283
Hypernatremia, 283
Hyperparasitemia, 282
Hypoalbuminemia, 269
and dengue, 155
Hypocalcemia, 283
Hypokalemia, in dengue, 153
Hyponatremia, 283
Hypovolemia, 44

I
Iberiotoxin, 114
IL-18, 66
Immune complex-mediated glomerulonephritis, 187
Immunofluorescence, 281
Immunoglobulin A (IgA), 230
Indinavir, 185, 190
Infections
bladder, 332
in kidney transplant recipients, 371
Infectious vasculitis, *see* Leptospirosis
Inflammatory and autoimmune diseases, 10
Inflammatory biomarkers, 45
Influenza A
epidemiology, 211
kidney injury, 212
mortality, 212
nephrotoxicity, 211
outcome, 212–213
treatment, 212–213
Inherent factors, 10
Interstitial fibrosis, 45
Interstitial kidney damage, 44
Interstitial nephritis, 332
Intestinal polyps, 228
Iohexol, 352
Iron deficiency, 46
Irukandji syndrome, 134

J
Jaundice, 317
Jellyfish, 131, 135

K
K+ channels bloackade, 115
Kala-azar, *see* Visceral leishmaniasis (VL)
Kaliotoxin, 114
Kidney complications, 270
Kidney Disease Improving Global Outcomes (KDIGO) guidelines, 206, 353
Kidney diseases
and schistosomiasis, 225
in tropical regions, 5
Kidney fibrosis, 45
Kidney function
assessment, 356
clinical assessment of, 352
Kidney Improving Global Outcomes (KDIGO) guidelines, 185
Kidney injury, 271–276
characteristics, 315
Kidney injury molecule 1 (KIM-1), 45, 47, 272, 280
Kidney replacement therapy (KRT), 359
Kidney stones, 33
and climate change, 34–35
formation, 33
Kidney transplant patients, with dengue fever, 154
Kidney transplant recipients
and arboviruses dengue, 380
and Chagas disease, 378
and chikungunya, 380, 381
and dengue, 380, 381
donor and recipient screening, 382
infection
and kidney graft, 374
clinical presentation, 372–373
immunosuppressive drugs, 373, 374
incidence, 371
peculiarities in treatment, 373–374
prevention, 374–377
transmission routes, 372
vaccines, 375
and leishmaniasis, 378
and strongyloidiasis, 383–384
and tuberculosis, 377–378
and zika, 380, 382
Kidney transplantation, 191
KIM-1, 66, 68
Korean hemorrhagic fever, 165

L
Latent tuberculosis reactivation (LTBI), 376
Lead, 47, 51
  and acute kidney injury, 51
  and arterial hypertension, 53
  chronic kidney disease, 52
  and endothelial cells, 52
  and interstitial fibrosis, 51
  poisoning with nephropathy, 51
  proximal tubules with Fanconi syndrome, 52
Leishmania, 254
  biological cycle of, 255
  life cycle, 269
  in kidney tissue, 271
  pathogenesis, 255–256
Leishmaniasis, 268, 372
  epidemiology, 254–255
  and kidney transplant recipients, 378
  prevalence, 253
  transmission through kidney grafts, 376
Leprosy
  acute kidney injury, 310
  biomarkers, 309, 311
  characteristics, 307
  chronic kidney disease and, 309
  clinical manifestations, 308–311
  epidemiology, 307–308
  hemodialysis, 311
  multibacillary, 312
  oxidative stress, 309
  pathophysiology, 308
  paucibacillary, 311
  prevalence, 307
  renal impairment in, 308, 310
  treatment, 310
Leptospirosis, 8, 10
  antibiotics in, 320
  antimicrobial prophylaxis, 321
  CKDu, 364
  clinical picture, 316–317
  diagnosis, 317
  diagnostic tests, 318
  epidemiology, 315–318
  global distribution, 315
  immunohistopathology, 319
  incidence, 316
  jaundice, 317
  kidney injury in, 318–319
  kinetics, 318
  laboratory findings, 317
  pathogenic species of, 315
  serologic testing, 318
  transmission, 315–318
  treatment, 319–321
  tubular alterations in, 319
Lethal isopropyl alcohol poisoning, 69
Leukocyturia, 333
Liposomal amphotericin B, 263
Liposomes, 271
Lithiasis, 33–35
Lithium
  bipolar disorder, 53
  toxicity, 53
Lithium carbonate, 65
Lonomia obliqua, 139
Lonomism
  bleeding episodes, 141
  characteristics, 139
  clinical and hemorrhagic manifestations, 140
  diagnosis, 141
  epidemiology, 139–140
  laboratory tests, 141
  lethality, 142
  prognosis, 142
  treatment, 142
  venom mechanism of action, 140
Loop of Henle, 354
Loop-mediated isothermal amplification (LAMP), 318
Loxosceles species, 121
Lutzomyia, 254
Lymphatic edema, 242
Lymphatic filariasis (LF), 249
  in Africa, 239, 240
  in America, 239
  in Asia, 239
  in Brazil, 240
  causes, 239
  characteristics, 239
  clinical manifestations, 241–242
  clinical presentation, 239
  diagnosis, 242–243
  distribution of, 240
  epidemiology, 240
  evolutionary cycle, 240–241
  renal involvement, 244
  in subtropical areas, 240
  treatment, 243
  tropical disease, 239

M
Maca, 80
Macrophage activation syndrome, 281
Maitotoxin, 132
Malaria, 8, 10, 372
  in acute kidney injury, 280
  and AKI
    clinical manifestations, 280
    pathogenesis, 280
    prevalence, 280
  clinical manifestations, 279
  dialysis and AKI, 285
  and glomerulopathies, 281–283
  hydroelectrolytic changes in, 283
  prevalence, 279
  and risk factors for AKI, 12
  treatment, 284–286
Malathion exposure, 54

Mammalian target of rapamycin (mTOR), 373
Margotoxin, 114
Marine toxins
  composition, 132–135
  epidemiology, 131
  kidney injury induced by, 133
  nephrotoxicity, 132–135
  venom application, 135
Mascarenotoxins, 88
Maurotoxin, 114
Measles, 372
Megaureter, 333
Membranoproliferative glomerulonephritis (MPGN), 188, 199, 204, 230, 231, 245, 282
Membranoproliferative glomerulonephritis without cryoglobulinemia, 204
Membranous glomerulonephritis, 340
Membranous glomerulopathy, 48, 188, 204
Membranous nephropathy (MN), 231
Membranous-proliferative glomerulonephritis, 282
Mercury contamination
  in Amazon, 47
  and autoimmune diseases, 49
Mesalamine suppository therapy, 344
Mesangium, 281
Metallothionein (MT), 47, 49
Methanol poisoning, 69
Methicillin-resistant *Staphylococcus aureus* (MRSA), 304
Methicillin-susceptible staphylococcus (MSSA), 302
Methyl salicylate, 79
Microalbuminuria, 271
Microalgae, 89
Microangiopathies, 282
Microfilaremia, 242
Microfilariae, 242
Microfilaruria, 248
Milky urine, 244
Miltefosine, American cutaneous leishmaniasis, 263
Modification of diet in renal disease (MDRD), 353
Monocyte chemotactic protein-1 (MCP-1), 272
Mosquito, 161
Mosquito bite, 148, 152, 155
Mushrooms, and nephrotoxicity, 80
Mycobacterium tuberculosis, 331
Myoglobinuria, 154, 326
Myotoxins, 127

N
N-acetyl-β-D-glucosaminidase (NAG), 47
National Kidney Foundation, 82
Natural disasters, 5
Neglected tropical diseases (NTDs), 3, 21, 24
Nephritis-associated plasmin receptor (NAPlr), 293
Nephrolithiasis, 34
Nephrologists, 13
Nephrologists shortage, 7
Nephropathy, 282
Nephrotic syndrome, 48, 282, 342
Nephrotoxic agents, 43
Nephrotoxicity, 79, 271
  environmental pollution and, 46
  lead, 51
  pathophysiology of, 45
  related to HIV treatment, 186
Neurotoxins, 127
Neutrophil gelatinase-associated lipocalin (NGAL), 47, 66, 68, 272, 273, 280
NK cells, 255
Non-infectious exposures, 9
Non-nephrotic proteinuria, 232
Noxiustoxin, 114

O
Obesity, 42
Obstetric complications, 9
Obstructive uropathy, 336
Occupational exposure, to silica, 53
Oligoanuria, 280
One Health approach, 10
Organ transplantation, 332–336
Organic anion transporter 1 (OAT1) channels, 189
Organic solvents, 53–54
Organochlorines (OC), 68
Organophosphates (OPs), 67
Orthohantavirus infection, 165
  antiviral drugs, 174
  convalescent phase, 169
  diagnosis, 169–171
  differential diagnosis, 170–171
  epidemiological surveillance actions, 175–176
  epidemiology, 167–168
  geographical distribution, 166
  HFRS clinical manifestations, 168–169
  hypotensive phase, 169
  incubation period, 168
  laboratory diagnosis, 170
  nonspecific laboratory diagnosis, 170
  pathophysiology, 171–172
  prevalence, 166
  prevention and control, 174
  renal involvement, 172
  reverse transcription-polymerase chain reaction, 170
  treatment, 173–174
  virions, 166
Ostreocins, 88
Ovatoxin-a, 88
Ovatoxins, 88
Ozone (O3) exposure, 46

P
Pacu, 86
Palytotoxin, 132
Palytoxin, 87, 88, 132
Pancytopenia, 269

Paraquat, 65
Parenteral systemic therapy, 262–263
Paroxysmal foodborne toxic rhabdomyolysis, 85
Particulate matter, 46
Penicillin, 319
Pentamidine, 263
Pentoxifylline, American cutaneous leishmaniasis, 263
Perforin, 132
Pericapsular fibrosis, 44
Peritoneal dialysis, 302
Pesticide
  and oxidative stress, 54
  poisoning, 54, 67
Phlebotomus, 254
Phospholipase A2, 127
Phthalates, 55
Picornaviridae, 195
Pirapitinga, 86
Plant toxins, 9
Plasma osmolarity, 355
Plasmodium, 279
Plasmodium falciparum, 281
Plasmodium malariae, 282
Plasmodium vivax, 282–283
Pneumocystis, 190
Polyarteritis nodosa, 200, 201
Polyclonal hypergammaglobulinemia, 270
Polyfluoroalkyl compounds (PFAS), 47
Polymerase chain reaction (PCR), 256, 317
Polystyrene microplastics, 55
Post-malaria hepatitis, 283
Post-streptococcal glomerulonephritis (PSGN), 291
  acute, 294
  in adults, 295
  in children, 296
  clinical/immunological pattern, 291
  after COVID-19 vaccination, 296
  diagnosis, 295
  in elderly, 295
  epidemics, 292
  epidemiology, 291–293
  etiology, 292
  histological finding, 294
  histopathology, 294–296
  with IgA deposition, 293
  by immune complexes, 293
  immunofluorescence findings, 295
  long-term prognosis, 297
  outbreaks, 292
  outcome, 296
  pathophysiology, 293–294
  post covid, 296–297
  prevalence, 293
  prognosis, 296
  stages of, 295
  treatment, 296, 297
Posttransplant glomerular disease, 191
Primaquine, 283
Procyclic promastigotes, 269
Proteinuria, 45, 153, 246, 247, 333, 340
  of glomerular origin, 247
  occurrence of, 341
  overload, 248
  reducing effects, 343
  regression of, 344
  remission of, 344
  with syphilis, 342
  tubular, 247
Pseudo-nitzschia, 132
PsTX-T toxin, 134
Pulmonary infection, 332
Pyelography, 336

R

Raw carp bile, 9
Red ants, 127
Rehmannia-6, 78
Relative risk index (RRI), 189
Renal amyloidosis, 309
Renal damage, 43
  biomarkers, 53
Renal function, 351–353
Renal impairment, in tuberculosis, 332
Renal lithiasis, 33
Renal replacement therapy (RRT), 141
Renal syndromes, and herbal medicine, 81
Renal tuberculosis
  and chronic kidney disease, 335–336
  clinical manifestations, 333
  computed tomography of patient with, 334
  and glomerulopathies, 335
  invasive procedures, 337
  laboratory assessment, 336
  pathophysiology of, 332–333
  renal biopsy of patient with, 334
  resistance to, 337
  treatment, 336
  treatment in advanced renal failure, 337
  treatment regimen in Brazil, 336
Renal vasoconstriction, 114
Retinol-binding protein (RBP), 47, 50
Rhabdomyolysis, 128, 134, 326, 328, 344
  Haff disease, 88
  and snakebite, 106
  spider venom and AKI, 121
  syphilis, 341
Ribavirin, 174
Ritonavir-boosted protease inhibitor (RTV/PI), 189

S

Salivary urea nitrogen dipstick (SUN), 366
Saponins, 79
Schistosoma mansoni, 230
  evolutionary cycle, 227
Schistosomiasis
  acute kidney injury, 233–234

acute phase, 228
antiparasitic drugs, 234
biomarkers of kidney injury, 233–234
causes, 225
chronic phase, 228
clinical manifestations, 227–229
clinical presentation, 232
diagnosis, 229
distribution in Brazil, 226
epidemiology, 225–226
evolutionary cycle, 226
glomerulopathy, 229–230
hepatointestinal, 228
hepatosplenic, 228, 232
hepatosplenic form, 228
histopathological findings, 231–232
intestinal, 228
and kidney disease, 225
laboratory tests, 229
morbidity, 226
mortality, 226
nephropathy, 232
pathophysiology, 230–231
prevalence, 226
renal histopathological findings, 232
tubular involvement, 233
urinary MCP-1 levels, 233
vasculopulmonary form, 228
Schistosomiasis mansoni
clinical forms, 229
diagnostic methods, 229
Scorpion stings
clinical applications, 116
clinical manifestations, 116
epidemiology, 113
nephrotoxicity, 114–115
treatment, 116
venom components, 114
Scyfosoas, 132
Sea anemones, kidney injury induced by, 134
Segmental and focal glomerulosclerosis, 281, 341
Sepsis
according to SIRS, 303
and AKI, 303
Silica
kidney injury, 53
occupational exposure, 53
Silicosis, 53
Smoking, 49
Snakebite envenomation
accidents with, 98
in Brazil, 97–99
and CKD, 107–108
incidence of, 98
kidney injury in, 106–107
Snakebites, 9
Snakes poisoning and kidney injury, 100
Socioeconomic factors, 7
Sodium-dependent dicarboxylate transporter member 3 (SLC13A3), 363
Solenopsins, 127
Solenopsis genus, 127
Solute-free water transport, 355
Sphingomyelinase D (SMase D), 122, 124
Spider venom
applications, 124
composition, 122
glomerular involvement, 123
induced kidney injury, 122, 123
nephrotoxicity, 122
treatment, 124
Staphylococcus
and acute kidney injury
pathophysiological mechanisms, 303
sepsis, 303
associated glomerulonephritis, 304
characteristics, 301
and chronic kidney disease, 302
coagulase-positive, 301
and immune-mediated diseases, 304
methicillin-resistant, 301
occurrence, 302
and peritoneal dialysis, 302–303
progression, 301
vancomycin, 304
Staphylococcus aureus, 301, 302
Streptococcal infection, GNDA due to, 291
Streptococcal pyrogenicexotoxin B (SPEB), 293
Streptomycin, 337
Strongyloidiasis, 372
and kidney transplant recipients, 383–384
Sulfadiazine, 191
Sulfamethoxazole, 191
Sulfamethoxazole-trimethoprim, 191
Syphilis
causes, 339
co-infections, 342–343
co-infections with HIV, 343
congenital, 342
epidemiology, 339–340
immunohistopathological findings in, 343–344
kidney abnormalities in, 342
kidney changes in, 342–343
kidney lesion in, 340
mechanisms of kidney injury in, 340
membranous glomerulonephritis, 340
renal changes, 341
rhabdomyolysis in, 341
stages of, 340
tertiary, 344

T

Tambaqui, 86
Taxus celebica, 80
Telemedicine, 12–14
Tenofovir, 184, 189

Tetanus
accidental, 324
and acute kidney injury, 326
cephalic, 325
characteristics, 323
classification, 324
clinical manifestations, 325–326
diagnosis, 326
epidemiology, 324–325
with formaldehyde, 323
incidence, 324
medical care, 328
mortality, 325
neonatal, 324
non-neonatal tetanus, 325
nutritional therapy, 328
pathophysiology, 325, 327
treatment, 327
vaccination, 324
Th1 response pattern, 255–256
Th2 response pattern, 256
THAI-LEPTO score, 11
Thrombotic microangiopathies (MAT), 187, 282
Tityus, 113
Tityustoxin, 114
TNFR-1, 66
TNFα, 45
Toxic alcohols, 69
Toxic injury, 43
Toxic rhabdomyolysis, 91
Toxoplasmosis, 372
Traditional Chinese medicine, 78
Transtubular potassium gradient (TTKG), 355
Treponema pallidum, 339
Tricyclic antidepressants, 65
Tripterygium wilfordii, 79
Tropical disease
Chagas disease, 217
lymphatic filariasis, 239
Tropical plant toxins, 9
Tropical pulmonary eosinophilia (TPE), 239
Tropical renal diseases, 4, 5
Tropics geography, 3
Trypanosoma cruzi, 378
Trypanosomiasis-induced glomerulonephritis, 219
Tuberculosis (TB), 372, 376
causes, 331
epidemiology, 331
incidence, 331
after organ transplantation, 377
renal impairment in, 332
Tuberculous pyelonephritis and pyonephrosis, 332
Tubular alterations, 355
Tubular function assessment, 354–356
Tubular necrosis, 114–116, 122, 134
Tubulointerstitial disorder, 33
Tubulointerstitial nephritis, 53, 271, 318, 319, 341

U
Uncaria tomentosa, 79
Urinalysis, 90
Urinary acidifica- tion processes, 259
Urinary acidification test, 355
Urinary biomarkers, 53
Urinary concentration test, 356
Urinary exosomes, 261
Urinary sediment analysis, 336
Urine/plasma osmolarity ratio, 355
Uromodulin, 47, 50

V
Vancomycin, 304
Venomous snakes, 98
Viral hepatitis, 195
and characteristics of kidney involvement, 208
Virchowian (multibacillary) form, 308
Viremia, 381
Visceral leishmaniasis (VL)
AKI in, 267
causes, 267
clinical manifestations, 269–270
diagnosis, 270
diagnostic tests, 270
epidemiology, 268–269
glomerular injury in, 271
kidney injury in, 267, 275
kidney involvement in, 271
life cycle, 269
pathophysiology of kidney injury in, 275
treatment, 270–271
worldwide endemicity, 268
Volemia, 283
Voltage-gated potassium channel (KCNA10) polymorphisms, 363

W
Wasp and bee stings, 9
Wegener's granulomatosis (WG), 305
Weight-loss supplements, 81
Weil's syndrome, 315, 318
Western blot, 261, 262
Wuchereria bancrofti, 239, 246

X
Xenobiotics, 47

Y
Yacon, 80
Yellow fever
characteristics, 161
clinical manifestations, 162

diagnosis, 162
epidemiology, 161–162
kidney biopsy findings, 163
pathophysiology of renal involvement, 162–163
treatment, 163

Z
Zika, 155
epidemiology, 156
and kidney transplant recipients, 157, 380–383
laboratory tests, 156
pathophysiology of renal involvement, 157
renal involvement, 156
treatment, 157
Zoonosis diseases, 11